

**POLICIES TO SPUR INNOVATIVE MEDICAL
BREAKTHROUGHS FROM LABORATORIES
TO PATIENTS**

HEARING
BEFORE THE
SUBCOMMITTEE ON RESEARCH AND TECHNOLOGY
COMMITTEE ON SCIENCE, SPACE, AND
TECHNOLOGY
HOUSE OF REPRESENTATIVES
ONE HUNDRED THIRTEENTH CONGRESS

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CONTENTS

July 17, 2014

Witness List	Page 2
Hearing Charter	3

Opening Statements

Statement by Representative Larry Bucshon, Chairman, Subcommittee on Research and Technology, Committee on Science, Space, and Technology, U.S. House of Representatives	7
Written Statement	9
Statement by Representative Daniel Lipinski, Ranking Minority Member, Subcommittee on Research and Technology, Committee on Science, Space, and Technology, U.S. House of Representatives	11
Written Statement	13
Statement by Representative Lamar S. Smith, Chairman, Committee on Science, Space, and Technology, U.S. House of Representatives	15
Written Statement	16

Witnesses:

Dr. Harold Varmus, Director, National Cancer Institute (NCI) at the National Institutes of Health (NIH)	
Oral Statement	18
Submitted Biography	21
Dr. Marc Tessier-Lavigne, President and Carson Family Professor, Laboratory of Brain Development and Repair, The Rockefeller University	
Oral Statement	30
Written Statement	32
Dr. Jay Keasling, Hubbard Howe Jr. Distinguished Professor of Biochemical Engineering, University of California, Berkeley; Professor, Department of Chemical & Biomolecular Engineering, University of California, Berkeley; Professor Department of Bioengineering, University of California, Berkeley; Director, Synthetic Biology Engineering Research Center	
Oral Statement	39
Written Statement	41
Dr. Craig Venter, Founder, Chairman, and Chief Executive Officer, J. Craig Venter Institute, Synthetic Genomics, Inc., and Human Longevity, Inc.	
Oral Statement	46
Written Statement	48
Discussion	57

Appendix I: Answers to Post-Hearing Questions

Dr. Harold Varmus, Director, National Cancer Institute (NCI) at the National Institutes of Health (NIH)	70
Dr. Marc Tessier-Lavigne, President and Carson Family Professor, Laboratory of Brain Development and Repair, The Rockefeller University	78

IV

	Page
Dr. Jay Keasling, Hubbard Howe Jr. Distinguished Professor of Biochemical Engineering, University of California, Berkeley; Professor, Department of Chemical & Biomolecular Engineering, University of California, Berkeley; Professor Department of Bioengineering, University of California, Berkeley; Director, Synthetic Biology Engineering Research Center	81
Dr. Craig Venter, Founder, Chairman, and Chief Executive Officer, J. Craig Venter Institute, Synthetic Genomics, Inc., and Human Longevity, Inc.	83

Appendix II: Additional Material for the Record

Statement submitted by Representative Eddie Bernice Johnson, Ranking Member, Committee on Science, Space, and Technology, U.S. House of Representatives	88
Letter submitted by Representative Larry Bucshon, Chairman, Subcommittee on Research and Technology, Committee on Science, Space, and Technology, U.S. House of Representatives	90
Article submitted by Representative Dana Rohrabacher, Committee on Science, Space, and Technology, U.S. House of Representatives	91

**POLICIES TO SPUR INNOVATIVE MEDICAL
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TO PATIENTS**

THURSDAY, JULY 17, 2014

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON RESEARCH AND TECHNOLOGY,
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY,
Washington, D.C.

The Subcommittee met, pursuant to call, at 9:05 a.m., in Room 2318 of the Rayburn House Office Building, Hon. Larry Bucshon [Chairman of the Subcommittee] presiding.

LAMAR S. SMITH, Texas
CHAIRMAN

EDDIE BERNICE JOHNSON, Texas
RANKING MEMBER

Congress of the United States
House of Representatives

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

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Subcommittee on Research and Technology

***Policies to Spur Innovative Medical Breakthroughs from
Laboratories to Patients***

Thursday, July 17, 2014
9:00 a.m. to 11:00 a.m.
2318 Rayburn House Office Building

Witnesses

Dr. Harold Varmus, Director, National Cancer Institute (NCI) at the National Institutes of Health (NIH)

Dr. Marc Tessier-Lavigne, President and Carson Family Professor, Laboratory of Brain Development and Repair, The Rockefeller University

Dr. Jay Keasling, Hubbard Howe Jr. Distinguished Professor of Biochemical Engineering, University of California, Berkeley; Professor, Department of Chemical & Biomolecular Engineering, University of California, Berkeley; Professor Department of Bioengineering, University of California, Berkeley; Director, Synthetic Biology Engineering Research Center

Dr. Craig Venter, Founder, Chairman, and Chief Executive Officer, J. Craig Venter Institute, Synthetic Genomics, Inc., and Human Longevity, Inc.

**U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
SUBCOMMITTEE ON RESEARCH AND TECHNOLOGY**

HEARING CHARTER

Policies to Spur Innovative Medical Breakthrough from Laboratories to Patients

**Thursday, July 17, 2014
9:00 a.m. - 11:00 a.m.
2318 Rayburn House Office Building**

Purpose

On Thursday, July 17, 2014, the Subcommittee on Research and Technology will hold a hearing to explore public and private sector efforts in basic, applied, translational, and clinical scientific research for medical breakthroughs discovered through interdisciplinary biomedical R&D combined with chemistry, physics, mathematics, computing, and engineering. The hearing will explore what public policies may spur more innovation and investment for medical breakthroughs.

Witnesses

Dr. Harold Varmus, Director, National Cancer Institute at the National Institutes of Health

Dr. Marc Tessier-Lavigne, President and Carson Family Professor, Laboratory of Brain Development and Repair, The Rockefeller University

Dr. Jay Keasling, Hubbard Howe Jr. Distinguished Professor of Biochemical Engineering, University of California, Berkeley; Professor, Department of Chemical & Biomolecular Engineering, University of California, Berkeley; Professor Department of Bioengineering, University of California, Berkeley; Director, Synthetic Biology Engineering Research Center

Dr. Craig Venter, Founder, Chairman, and Chief Executive Officer, J. Craig Venter Institute, Synthetic Genomics, Inc., and Human Longevity, Inc.

Hearing Overview

Understanding and treating disease and injury remains one of the most challenging problems facing the scientific community. Progress in the biological sciences has enjoyed a long symbiotic relationship with the physical and mathematical sciences; for example, physicists such as Lord Rayleigh, Hermann Helmholtz and Erwin Schrödinger made fundamental contributions to our understanding of physiology and medicine.¹

¹From Photons To Perception: A Physicist Looks At The Brain, Dr. William Bialek. Available From <http://online.itp.ucsb.edu/lecture/bialek/>

Biomedical research has been crucial to advancing our understanding of cures to complex human diseases and injury. Publicly-funded biomedical research is estimated at approximately \$50 billion annually (with the NIH budget \$30.1 billion in FY2014), while privately-funded biomedical research in the U.S. is estimated at over \$70 billion annually.²

Medical sciences research is becoming an increasingly interdisciplinary field, with important contributions from fields as diverse as the chemistry, physical sciences, applied mathematics, computer science, and engineering,³ fields which have enjoyed public funding support from the National Science Foundation (NSF). Each of these disciplines has furthered our understanding of biological mechanisms, thereby allowing researchers to move towards an integrated picture of the human body. In FY 2014, NSF's budget for the Biological Science Directorate is over \$720 million, with several other Directorates also funding biological-related research.

One aspect of biomedical research for medical breakthroughs involves the creation of new drugs and vaccines. In the past 40 years, 153 FDA-approved drugs, vaccines, and new starts for existing drugs were discovered from research done at public sector research institutions (PSRIs). Moreover, roughly 10-20% of all drugs involved in new-drug applications approved between 1990-2007 were the result of research performed by PSRIs. Of the 252 new drugs approved by the FDA between 1998 and 2007, 31% of the 118 drugs were considered "scientifically novel" and a result of research originally performed at universities.⁴ Over the FY2002-FY2012 time period, \$917.7 million in royalties were generated from licenses on NIH-owned patents⁵. To leverage these Federal investments, legislation such as the Stevenson-Wydler Act and Bayh-Dole Act have facilitated the commercialization of government-funded R&D, through policies that encourage collaboration between government, universities, and industry.

Modern advances in the physical, mathematical, engineering and computer sciences have also converged to create new research fields that advance biomedical science. One such example is the field of *synthetic biology*, where living systems are seen as building blocks that can be retrieved from their natural context, reshaped, standardized for a given specification and then repurposed for a specific task such as making a drug.⁶

Synthetic biology represents a new approach to biological engineering, a key enabling technology with the potential to fundamentally change the approach, tools and techniques of modern biological research and innovation, to the benefit of society. Because of its

² <http://www.nejm.org/doi/full/10.1056/NEJMp1311068>

³ <http://www.cancer.gov/aboutnci/director/speeches/impact-of-physics-1999>

⁴ <http://www.nejm.org/doi/pdf/10.1056/NEJMsa1008268>
http://news.heartland.org/sites/all/modules/custom/heartland_migration/files/pdfs/28819.pdf

⁵ Federal R&D, Drug Discovery, and Pricing: Insights from the NIH-University-Industry Relationship, CRS Report, November 30, 2012

⁶ "Synthetic Biology", Discover Magazine, October 2013, Vol 34, No 8, pp 48-54.

interdisciplinary nature, this field has the potential to enhance many industrial sectors beyond medicine, including agriculture and environmental remediation.⁷

Economic Impact

The economic implications for scientific research that can cure or alleviate the effects of human diseases or injuries is significant. For example, the monetary cost of dementia, including Alzheimer's disease, in the United States ranges from \$157 billion to \$215 billion annually. The House Research and Technology Subcommittee held a hearing in July 2013 to discuss interdisciplinary brain science research.

Incentives for innovation in the industrial community clearly have contributed to substantial research and development by the biopharmaceutical and biotechnology sectors. In 2012, research and development spending by the biopharmaceutical industry in the United States totaled around \$63.1 billion.⁸ Domestic R&D spending for members of the Pharmaceutical Research and Manufacturers of America (PhRMA) was an estimated \$37.5 billion, with 22.7% of domestic sales reinvested in research and development.⁹ U.S. biotechnology companies spent \$19.3 billion on R&D, and produced \$63.7 billion in revenue in 2012.¹⁰ For an industry that practically did not exist 30 years ago, biotechnology in the United States has provided new products and processes for the international marketplace, including more than 300 biotech drugs and vaccines.¹¹

Issues for Consideration

The science community has a number of metrics aimed at measuring scientific quality, including the number of publications, citations, Nobel Prizes, society-specific honors, and others. Economic output metrics, on the other hand, have proven more difficult to gather and characterize and have been challenging for policymakers seeking to develop research and development (R&D) policy decisions. Given the desire for more evidence-based budgeting of R&D, recent analysis has shown that there were meaningful differences in the rate and quality of patenting across NIH from 2003 to 2012.¹² Patents are positively correlated with higher levels of regional employment, start-up companies, and greater economic impact, and may be a useful metric for policymakers when assessing effectiveness of public investment.

⁷ "Next Steps for European synthetic biology: a strategic vision from ERASynBio" Report, April 2014. Available From <http://www.bbsrc.com/web/FILES/Publications/1404-era-synbio-strategic-vision.pdf>

⁸ Bureau of Economic Analysis, U.S. Department of Commerce, National Income and Product Accounts Tables, Table 5.6.5. Private Fixed Investment in Intellectual Property Products by Type. Available From <http://www.bea.gov/iTable/iTable.cfm?ReqID=9&step=1#reqid=9&step=3&isuri=1&903=331>

⁹ 2014 Profile: Biopharmaceutical Research Industry, PhRMA, "Key Facts," and p. 74, http://www.phrma.org/sites/default/files/pdf/2014_PhRMA_PROFILE.pdf

¹⁰ Beyond Border: Matters of Evidence, Biotechnology Industry Report 2013, Ernst and Young. Available From [http://www.ey.com/Publication/vwLUAssets/Beyond_borders/\\$File/Beyond_borders.pdf](http://www.ey.com/Publication/vwLUAssets/Beyond_borders/$File/Beyond_borders.pdf)

¹¹ "The Biopharmaceutical Industry: Creating Research, Progress and Hope". Available From http://www.phrma.org/about/biopharmaceutical_sector

¹² Kalutkiewicz M, Ehman R, "Patents as Proxies: NIH hubs of innovation" *Nature Biotechnology* 32, 536–537 (2014). Available From <http://www.nature.com/nbt/journal/v32/n6/abs/nbt.2917.html>

Rothwell, J. et al. Patenting Prosperity: Invention and Economic Performance in the United State and its Metropolitan Areas (Brookings Institution; February 2013). Available From <http://www.brookings.edu/research/reports/2013/02/patenting-prosperity-rothwell>

There are also significant concerns that R&D budgets—especially for the pharmaceutical industry—are being cut in private sector companies in order to return profits to their shareholders.¹³ R&D investments often represent the long-term seed corn for future breakthroughs, while profit-taking is short-term gain for the shareholders. Thus, leadership within companies must carefully balance short-term and long-term interests of the company and their shareholders.

Many pharmaceutical companies have developed alternative means of acquiring new technologies, including an increasing number of alliances between large businesses, small companies, government laboratories, research hospitals, and universities.¹⁴ Such partnerships can augment funding sources from private and public sectors, increase technology transfer, stimulate additional innovation, lead to new products and processes, and expand markets. On the other hand, such collaborations have some downsides such as unfair advantages and conflicts of interest, among others.¹⁵

¹³ “Do Drug Companies Make Drugs, or Money” June 2, 2014 New York Times. Available From http://dealbook.nytimes.com/2014/06/02/do-drug-companies-make-drugs-or-money/?_php=true&_type=blogs&_r=0

¹⁴ Patricia M. Danzon, Sean Nicholson, Nuno Sousa Pereira, Productivity in Pharmaceutical-Biotechnology R&D: The Role of Experience and Alliances, National Bureau of Economic Research, Working Paper 9615, April 2003, 5. Available From <http://www.nber.org/papers>. See also, Nadine Roijakkers and John Hagedoorn, "Inter-firm R&D Partnering in Pharmaceutical Biotechnology since 1975: Trends, Patterns, and Networks," Research Policy, April 2006, 444.

¹⁵ Federal R&D, Drug Discovery, and Pricing: Insights from the NIH-University-Industry Relationship, Wendy H. Schacht. Available From <http://www.crs.gov/pages/Reports.aspx?PRODCODE=RL32324&Source=search>

Chairman BUCSHON. Subcommittee on Research and Technology will come to order. Good morning. Welcome to today's hearing, entitled "Policies to Spur Innovative Medical Breakthroughs from Laboratories to Patients." I recognize myself for five minutes for an opening statement.

As a cardiothoracic surgeon and medical professional, I know firsthand there are many complexities surrounding the human body, and understanding human disease is one of the most challenging problems facing the scientific and medical communities. Complex human diseases will likely require an interdisciplinary and multifaceted approach, with the right scientific questions being asked and debated, with clear goals and endpoints being articulated.

The creative drive of American science is the individual investigator, and I have faith they will continue to tackle, understand, and contribute original approaches to these problems. Medical diseases such as cancer, Alzheimer's, Parkinson's, autism, epilepsy, dementia, stroke, and traumatic brain injury have an enormous impact, and enormous economic impact, and personal impact for affected Americans. For example, Alzheimer's disease is a severe form of dementia, and the sixth leading cause of death in the U.S. It affects both the 5.1 million Americans that have the disease and their friends and family, who must watch their loved ones suffer from its symptoms. The average annual cost of care for people with dementia over 70 in the U.S. is roughly between 157 and \$210 billion in 2010.

I want to stress my support for medical science research, in particular understanding diseases from an interdisciplinary perspective. As our witnesses will testify today, medical science has benefitted enormously from fields as diverse as applied mathematics, computer science, physics, engineering, molecular biology, and chemistry.

More important basic science research results from NSF funded research will be the future experimental tools for a hypothesis-based, data-driven research for brain science researchers. I also see this as an important opportunity for continuing interdisciplinary work between the various federal science agencies, including NSF, NIST, and NIH, and I hope to see more collaboration and productive research opportunities.

At the same time, I am interested in how private sector research can complement ongoing federal R&D investment, and what public policies may spur more innovation and investment from medical breakthroughs. Companies must carefully balance short term and long term interests of the company and their shareholders. Private sector research efforts use the results of basic science research in the physical, mathematical, and engineering sciences. For example, advances in computing have led to the development of software, with the goal of helping medical sciences make sense of cancer genomes.

Watson, an advanced computer that was developed by IBM is being enlisted not only to identify mutations from a patient's tumor biopsy in order to help understand how these mutations cause cancer, but also to produce a list of drugs that could potentially treat

the cancer. All of this can potentially be done in minutes, and I had a demonstration of Watson in my office. It was fascinating.

Our witnesses today reflect the wide spectrum of research in the biomedical sciences, and each have been recognized in their respective fields. I would like to thank the witnesses for their being here today, and taking time to offer their perspectives on this important topic. I hope you will continue to work with us to maximize federal funding of biomedical research. I would also like to thank the Ranking Member, Mr. Lipinski, and everyone else participating in today's hearing.

[The prepared statement of Mr. Bucshon follows:]



For Immediate Release
July 17, 2014

Media Contacts: Zachary Kurz
(202) 225-6371

**Statement of Research and Technology Subcommittee Chairman Larry Bucshon (R-Ind.)
Hearing on Policies to Spur Innovative Medical Breakthroughs from Laboratories to Patients**

Chairman Bucshon: I would like to welcome everyone to today's Research and Technology Subcommittee hearing on policies to spur the transfer of innovative medical breakthroughs from laboratories to patients.

As a cardio-thoracic surgeon and medical professional, I know firsthand there are many complexities surrounding the human body; and understanding human disease is one of the most challenging problems facing the scientific and medical communities. Complex human diseases will likely require an interdisciplinary and multifaceted approach with the right scientific questions being asked and debated with clear goals and endpoints being articulated. The creative drive of American science is the individual investigator, and I have faith they will continue to tackle, understand and contribute original approaches to these problems.

Medical diseases such as cancer, Alzheimer's, Parkinson's, autism, epilepsy, dementia, stroke, and traumatic brain injury have an enormous economic and personal impact for affected Americans. For example, Alzheimer's disease- a severe form of dementia and the sixth leading cause of death in the US- affects both the 5.1 million Americans that have the disease and their friends and family who must watch their loved one suffer from its symptoms. The average annual cost of care for people with dementia over 70 in the US was roughly between \$157 and \$210 billion dollars in 2010.

I want to stress my support for medical science research, in particular understanding diseases from an interdisciplinary perspective. As our witnesses will testify today, medical science has benefited enormously from fields as diverse as applied mathematics, computer science, physics, engineering, molecular biology, and chemistry. More importantly, basic science research results from NSF funded research will be the future experimental tools for hypothesis-based data-driven research for brain science researchers.

I also see this as an important opportunity for continuing interdisciplinary work between the various federal science agencies, including the NSF, NIST, and NIH and I hope to see more collaboration and productive research opportunities.

At the same time, I am interested in how private-sector research can complement on-going federal R&D investment, and what public policies may spur more innovation and investment for medical breakthroughs. Companies must carefully balance short-term and long-term interests of the company and their shareholders.

Private sector research efforts use the results of basic science research in the physical, mathematical and engineering sciences. For example, advances in computing have led to the development of software with

the goal of helping medical scientists make sense of cancer genomes. Watson, an advanced computer that was developed by IBM, is being enlisted not only to identify mutations from a patient's tumor biopsy in order to help understand how these mutations cause cancer but also to produce a list of drugs that could potentially treat the cancer. All this can potentially be done in a few minutes.

Our witnesses today reflect the wide spectrum of research in the biomedical sciences, and each has been a recognized in their respective fields. I'd like to thank the witnesses for being here today and taking time to offer their perspectives on this important topic. I hope you will continue to work with us to maximize federal funding of biomedical research. I'd also like to thank Ranking Member Lipinski and everyone else participating in today's hearing.

###

Chairman BUCSHON. At this point now I recognize the Ranking Member, the gentleman from Illinois, Mr. Lipinski, for his opening statement.

Mr. LIPINSKI. Thank you, Chairman Bucshon, for holding this hearing on policies to spur medical breakthroughs, something we all certainly want to do what we can here to make it as likely as possible to get those medical breakthroughs, and get them out to market and helping people. And I want to thank all of our witnesses for being here today. I look forward to your testimony.

Innovation, whether in biomedical research or elsewhere, is an ecosystem that is more than the sum of its parts. Federal agencies, universities, and research institutions, entrepreneurs, and the private sector all have important roles to play. That is why I am glad we have witnesses from across these sectors here to testify today.

In April we held a hearing in this committee on innovation prize competitions. We heard testimony about the need for a kidney prize to facilitate the development of more effective treatments for kidney disease and end stage renal disease. Innovation prizes, as well as other forms of pre-commercial support, such as proof of concept funding, and programs like NSF's Innovation Corps, which recently announced a collaboration with NIH, could hold great promise for future biomedical breakthroughs.

I hope that our panel could comment on these and other potential mechanisms for supporting technology transfer from the lab to the marketplace. And, of course, it bears repeating that our ability to innovate will be greatly limited without growing investments in the basic research that generates these technologies.

The emerging field of engineering biology has grown out of the decades old field of genetic engineering. In the 1800s, Gregor Mendel established many of the rules of heredity that became the foundation of modern genetics by studying pea plants. But even before Mendel, farmers knew that by cross-breeding animals and plants you could favor certain traits.

Since the 1970s, scientists have been using more advanced tools to directly insert new genes or delete genes from plant and microbio genomes. Engineering biology is the next step in this field, and is being accelerated by the development of technologies such as DNA sequencing, which has gone from taking years, and costing billions of dollars, to taking just days, and costing a few thousand dollars, which is truly amazing.

We have already started seeing commercial applications from engineering biology. I look forward to hearing more about how Dr. Keasling and his research group were able to engineer a microorganism to produce a life-saving anti-malarial drug that is now being produced on a large scale by a pharmaceutical company. I also look forward to learning about other potential applications from engineering biology research, including energy, agriculture, chemicals, and manufacturing.

Since this is an emerging field, and it could have significant economic benefit for the United States, it is important that we make the necessary federal investments in both the foundational research, and across the potential application areas. Several of the agencies under the Committee's jurisdiction have significant programs in engineering biology. The Department of Energy has one

of the largest programs focused on bioenergy. The National Science Foundation is investing more in this area, both through individual research awards, and through their support of an engineering research center at Berkeley. NASA and NIST also have programs in this area. And, of course, NIH and the Department of Agriculture are significant players in this research.

The nation would benefit not just from increased investment at individual agencies, but also from coordination of federal efforts under some kind of plan or strategy. Other countries have identified this area specifically as an important area to make investments in. The European Union's Europe 2020 strategy calls out this field as a key element as it develops a strategy and an action plan for investment.

I have never seen that one happen before. I didn't even run over time yet.

Chairman BUCSHON. That was your warning.

Mr. LIPINSKI. Don't worry, I am almost done. I am concerned if the United States does not take the necessary steps, we will lose our leadership position in this field. That was symbolic of losing our leadership position, the lights going out. We should also ensure that we are facilitating public/private partnerships. Given the potential of commercial applications across nearly all sectors of our economy, there is a need to engage and encourage private sector collaboration at a pre-competitive level. And, finally, we must pay careful attention to issues of human environmental safety and ethics when it comes to engineering biology research, including by supporting research on those topics.

I look forward to all witnesses' testimony, and the Q&A. Thank you all for being here, and I yield back the balance of my time.

[The prepared statement of Mr. Lipinski follows:]

OPENING STATEMENT

Ranking Member Daniel Lipinski
Subcommittee on Research & Technology
Committee on Science, Space, and Technology

Research & Technology Subcommittee Hearing
“Policies to Spur Innovative Medical Breakthroughs from Laboratories to Patients”

July 17, 2014

Thank you Chairman Bucshon for holding this hearing on policies to spur medical breakthroughs. I want to thank all the witnesses for being here today. I look forward to your testimony.

Innovation, whether in biomedical research or elsewhere, is about an ecosystem that is more than the sum of its parts. Federal agencies, universities and research institutions, entrepreneurs, and the private sector all have important roles to play. That’s why I’m glad we have witnesses from across these sectors here to testify today.

In May, we held a hearing in this subcommittee on innovation prize competitions where we heard testimony about the need for a kidney prize to facilitate the development of more effective treatments for kidney disease and end-stage renal failure. Innovation prizes, as well as other forms of pre-commercial support such as proof-of-concept funding and programs like NSF’s innovation Corps which recently announced a collaboration with NIH, could hold great promise for future biomedical breakthroughs. I hope that our panel can comment on these and other potential mechanisms for supporting technology transfer from the lab to the marketplace.

And of course it bears repeating that our ability to innovate will be greatly limited without growing investments in the basic research that generates these technologies.

The emerging field of engineering biology has grown out of the decades-old field of genetic engineering. In the 1800s, Gregor Mendel established many of the rules of heredity that became the foundation of modern genetics by studying pea plants. But even before Mendel, farmers knew that by crossbreeding animals and plants you could favor certain traits. Since the 1970’s scientists have been using more advanced tools to directly insert new genes or delete genes from plant and microbial genomes.

Engineering biology is the next step in this field, and is being accelerated by the development of technologies such as DNA sequencing—which has gone from taking years and costing billions of dollars to taking just days and costing a few thousands of dollars. That truly is amazing. We are already starting to see commercial applications from engineering biology. I look forward to hearing more about how Dr. Keasling and his research group were able to engineer a microorganism to produce a life-saving anti-malarial drug that is now being produced on a large scale by a pharmaceutical company. I also look forward to learning about other potential

applications from engineering biology research, including energy, agriculture, chemicals, and manufacturing.

Since this emerging field could have significant economic benefit for the United States, it is important that we make the necessary federal investments in both the foundational research and across the potential application areas.

Several of agencies under this Committee's jurisdiction have significant programs in engineering biology. The Department of Energy has one of the largest programs focused on bioenergy. The National Science Foundation is investing more in this area, both in individual research awards and through their support of an engineering research center at Berkeley. NASA and NIST also have programs in this area. And of course NIH and the Department of Agriculture are significant players in this research. The nation would benefit not just from increased investment at individual agencies but also from coordination of federal efforts under some kind of plan or strategy.

Other countries have identified this area specifically as an important area to make investments in. The European Union's Europe 2020 Strategy calls out this field as a key element and has developed a strategy and an action plan for investment. I am concerned that if the United States does not take the necessary steps, we will lose our leadership position in this field.

We should also ensure that we are facilitating public-private partnerships. Given the potential commercial applications across nearly all sectors of our economy, there is a need to engage and encourage private sector collaboration at a pre-competitive level. And finally we must pay careful attention to issues of human and environmental safety and ethics when it comes to engineering biology research, including by supporting research on those topics.

I look forward to all of the witness testimony and the Q&A, and I thank you all for being here today. I yield back the balance of my time.

Chairman BUCSHON. Thank you, Mr. Lipinski. I now recognize the Chairman of the full Committee, the gentleman from Texas, Mr. Smith, for his opening statement.

Chairman SMITH. Thank you, Mr. Chairman.

Basic biomedical research is increasingly interdisciplinary in nature. Advances in applied mathematics, physics chemistry, computer science, and engineering provide a better understanding of medical conditions, and the tools to help find cures. The National Science Foundation can play an important and vital role in understanding the basic science behind many debilitating conditions.

For example, developments in basic scientific research have provided deep insight into how the brain and other neurological structures are organized. NSF research could help us better understand conditions such as cancer, Alzheimer's, Parkinson's, autism, stroke, dementia, traumatic brain injury, epilepsy, and many other disorders. Countless lives have unfortunately been lost to these diseases, and the economic impact, physical and emotional toll they can put on families can make them even more devastating.

The National Science Foundation should support interdisciplinary research in conjunction with the National Institutes of Health to help us better understand medical illnesses. The Frontiers in Innovation, Research, Science and Technology Act, or FIRST Act, supports basic research that has the potential to improve the daily lives of millions of Americans. The FIRST Act increases funding for subjects such as math, physical sciences, biological sciences, computer sciences, and engineering for Fiscal Year 2015.

The FIRST Act, which was successfully reported out of Committee this past May, includes a \$270 million increase for Fiscal Year 2015 over current NSF spending for these important subject areas. Federally funded basic research has supported the creation of technologies that have changed and improved our daily lives, including the MRI and laser technology. Efficient and effective use of NSF funding geared toward basic research will help us better understand medical conditions, and lead to medical breakthroughs that benefit both doctors and patients alike.

Thank you, Mr. Chairman, for holding this hearing. And I want to say, at the risk of offending any other panel, we have an unusually distinguished panel of witnesses today, and we look forward to hearing from their testimony.

[The prepared statement of Mr. Smith follows:]



For Immediate Release
July 17, 2014

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**Statement of Chairman Lamar Smith (R-Texas)
Hearing on Policies to Spur Innovative Medical Breakthroughs
from Laboratories to Patients**

Chairman Smith: Basic biomedical research is increasingly inter-disciplinary in nature. Advances in applied mathematics, physics, chemistry, computer science and engineering provide a better understanding of medical conditions and the tools to help find cures.

The National Science Foundation (NSF) can play an important and vital role in understanding the basic science behind many debilitating conditions. For example, developments in basic scientific research have provided deep insight into how the brain and other neurological structures are organized.

NSF research could help us better understand conditions such as cancer, Alzheimer's, Parkinson's, autism, stroke, dementia, traumatic brain injury, epilepsy, and many other neurological disorders. Countless lives have unfortunately been lost to these diseases. And the economic impact and physical and emotional toll they can put on families can make them even more devastating.

The NSF should support inter-disciplinary research, in conjunction with the National Institutes of Health (NIH), to help us better understand medical illnesses.

The results of this research will have a clear and direct benefit to the American public. In my district in Fiscal Year 2013, the NIH funded 215 projects at the University of Texas Health Science Center at San Antonio totaling about \$70 million. Over the last 5 years, NSF funded \$44 million to universities and colleges in the San Antonio area.

The Frontiers in Innovation, Research, Science, and Technology Act, or FIRST Act, supports basic research that has the potential to improve the daily lives of Americans. The FIRST Act increases funding for subjects such as mathematics, physical sciences, biological sciences, computer sciences, and engineering for Fiscal Year 2015.

The FIRST Act, which was successfully reported out of Committee this past May, includes a \$270 million increase for Fiscal Year 2015 over current NSF spending for these important subject areas. Federally funded basic research has supported the creation of technologies that have changed and improved our daily lives — including the MRI and laser technology.

Efficient and effective use of NSF funding geared toward basic research will help us better understand medical conditions and lead to medical breakthroughs that benefit both doctors and patients alike. Thank you Mr. Chairman for holding this hearing, and I look forward to the witnesses' testimony.

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Chairman BUCSHON. Thank you, Chairman. At this point, if there are other Members who wish to submit additional opening statements, your statements will be added to the record.

[The prepared statement of Ms. Johnson appears in Appendix II]

Chairman BUCSHON. At this time I would like to introduce our witnesses, and it is a distinguished panel. Thanks for being here.

Our first witness is Dr. Harold Varmus, Director of the National Cancer Institute. He previously served for ten years as President of Memorial Sloan Kettering Cancer Center, and six years as Director of the National Institutes of Health. Dr. Varmus is a co-recipient of the Nobel Prize for studies on the genetic basis of cancer. Dr. Varmus was a co-chair of President Obama's Council of Advisors on Science and Technology. And Dr. Varmus majored in English, which I found interesting, Literature at Amherst, and earned a Master's Degree in English at Harvard, and is a graduate of Columbia University's College of Physicians and Surgeons. Welcome.

Our second witness is Dr. Marc Tessier-Lavigne. Did I say that right? President of the Rockefeller University, where he is also Carson Family Professor, and head of the laboratory of brain development and repair. Previously he served as Chief Scientific Officer of Genentech, a leading biotechnology company. He obtained undergraduate degrees from McGill and Oxford Universities, and a Ph.D. from the University College London, and was a post-doctoral fellow over there also, and at Columbia University. Prior to joining Genentech, he held faculty positions at the University of California San Francisco and at Stanford, where he was the Susan B. Ford Professor and Investigator with the Howard Hughes Medical Institute. Welcome.

Our third witness is Dr. Jay Keasling, the Hubbard Howe Jr. Distinguished Professor of Chemical and Biomolecular engineering, and Professor of Bioengineering at the University of California at Berkeley. He is the Director of the Synthetic Biology Engineering Research Center, Associate Laboratory Director for Biosciences at the Lawrence Berkeley National Laboratory, and Chief Executive Officer of the Joint Bioenergy Institute.

Dr. Keasling earned his Bachelor's Degree from the University of Nebraska, and his graduate degrees in Chemical Engineering from the University of Michigan. In 2006 he was cited by Newsweek as one of the country's 10 most esteemed biologists. Welcome.

And our fourth witness is Dr. Craig Venter, Founder, Chairman, and Chief Executive of the J. Craig Venter Institute, Synthetic Genomics, Incorporated, and Human Longevity, Incorporated. Dr. Venter contributed to sequencing the first draft human genome in 2001, the first complete diploid human genome in 2007, and the construction of the first synthetic bacterial cell in 2010. Dr. Venter is the recipient of the 2008 National Medal of Science.

Dr. Venter earned both a Bachelor's Degree in Biochemistry, and a Ph.D. in Physiology and Pharmacology from the University of California at San Diego. Thank you for being here.

And, again, thanks to all our witnesses. It is a very impressive panel, and I think this is going to be a great hearing. As our witnesses should know, spoken testimony is limited to five minutes, after which the Members of the Committee will have five minutes

each to ask questions. I now recognize Dr. Varmus for five minutes to present his oral testimony.

**TESTIMONY OF DR. HAROLD VARMUS, DIRECTOR,
NATIONAL CANCER INSTITUTE (NCI)
AT THE NATIONAL INSTITUTES OF HEALTH (NIH)**

Dr. VARMUS. Chairman Bucshon, Chairman Smith, Mr. Lipinski, and other Committee Members, I thank you for your strong, supportive opening statements, and for holding this important hearing about the state of the American scientific enterprise. This is a pivotal moment. On the one hand, our investments in science and technology continue to lead the world. Our discoveries and applications of knowledge have enriched the country, improved the world, and expanded opportunities for yet further discover and application.

But in recent years, we have been fiscally constrained. The place I work, the NIH, has lost 25 percent of its buying power over the last decade. We are able to support fewer than one in seven of our grant applications. In the meantime, other countries have quickened their pace of investment. Under these circumstances, the nation needs to determine how the parts of the enterprise can most effectively work together, and I take that to be the ultimate goal of this hearing.

But that isn't easy. The scientific landscape is complex, with at least four dimensions. First, many defined disciplines, which often intersect. Second, a spectrum of activities, from free ranging fundamental research, to more programmatic—or pragmatic efforts to use basic knowledge. Third, a variety of funding sources, including many government agencies, small and large companies, academic institutions, and private philanthropies. And fourth, several kinds of mechanisms to support research from each of our sources. Balancing these elements is of obvious interest to the Subcommittee and to your witnesses.

I would like to make four points about the landscape to help guide our discussion today. The first three are operating principles. The fourth illustrates some novel ways in which my agency, the NCI, has tried to increase our effectiveness.

First, the importance of interdisciplinary work, which has already been alluded to. Historically, major advances in medicine have been especially dependent on physical sciences—on physics and chemistry. The body is an object that can be studied with those tools. Just consider microscopes, X-ray machines, radio isotopes, pharmacology, electrocardiograms, Mr. Bucshon, and the electroencephalogram.

More recently, the studies of genomes that have been alluded to, proteins and cells, have revolutionized our understanding of normal and diseased human beings, thanks to inventions that required, again, physical, mathematics, engineering, and chemistry, as well as, importantly, computational science to handle the massive sets of data that we have accrued. Now newly launched initiatives, such as the President's BRAIN project, or the NCI's therapeutics efforts that are based on genetic signatures, so-called precision medicine, are going to require these in still other fields. In short, the future

of medicine will depend on maintaining the vibrancy and the interaction of allied fields of science and technology.

Second point, sustained fundamental research is essential for further developments in medicine. Yet, when financial support is highly competitive, as is the case now, the choice of research projects veers toward applications of existing knowledge, and away from basic science, posing a serious risk to future productivity.

I have mentioned that medicine is being transformed today by the unveiling of genetic blueprints, and by the identification of the specific damage that occurs in most human diseases, specifically like cancers. But discovery is not finished. Despite these enormous increases in knowledge, fundamental features of biological systems have yet to be discovered. We know this from some very recent examples, the discovery of unanticipated forms of RNA that perform functions other than its well-known roles in the synthesis of proteins, or the discoveries of enzymes from strange organisms that allow rapid and efficient re-engineering of genomes of many kinds of cells. Such unanticipated results and methods, and their subsequent applications, can come only from unfettered basic research.

The third point is that funders of research had aimed for a balanced and synergistic portfolio. Each component of the scientific landscape has a limited range of action, and government science agencies, academic institutions, and some charities have a strong mandate to invest in fundamental science.

Commercial entities are constrained from a deep commitment to unfettered basic research, but invest heavily in applied research, and these observations articulated over 70 years ago by Vannevar Bush have been the basis for the success of American science. But still, all these elements need to interact, and to learn where and how scarce resources are being committed, to engage in collaborative work, and to accelerate progress across the full spectrum of research and development.

Finally, the fourth point, which I will ask for some indulgence just to describe briefly, leaders of funding agencies, especially in government, can help in the situation by using their various mechanisms to encourage interdisciplinary team science to protect investigators working in—on fundamental studies, and to work with our funding partners, especially in these fiscally challenging times. The NCI has exploited the flexibility of our funding mechanisms in a variety of ways that are listed in my written testimony, just to mention a few extremely briefly.

The Cancer Genome Atlas Project has supported many hundreds of DNA sequences, geneticists, bioinformaticians, oncologists, and others to compile an extensive set of characteristics about over 20 different time—kinds of human cancer in a way that is now transforming the way we approach cancer patients through precision medicine.

Our Frederick National Laboratory for Cancer Research in Frederick, Maryland, a contract program modeled on—in part on the Department of Energy's national programs, carries out both general service functions through nanotechnology, and clinical collaboration with 19 other agencies, and specific projects, like a project that addresses a collection of genes known as rash genes that drive about a third of human tumors.

And, finally, our provocative questions exercise is intended to bring scientists of many disciplines together to identify the great unsolved, and sometimes not closely attended to, problems in a way that now allows us to fund proposals to answer those questions.

I will be pleased to answer any questions you might have. Thank you, Mr. Chairman.

[The prepared statement of Dr. Varmus follows:]

**Testimony
Before the
Subcommittee on Research and Technology
Committee on Science, Space, and Technology
United States House of Representatives**

**Statement of
Harold Varmus, M.D.
Director
National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services**

Thursday July 17, 2014

Chairman Bucshon, Mr. Lipinski, and other Committee members:

Thank you for conducting this important hearing that addresses critical issues about the state of the American scientific enterprise.

This is a pivotal moment for our enterprise. On the one hand, the United States continues to lead the world in its investments, both public and private, in most fields of science and technology; and its discoveries and applications of scientific knowledge have enriched the country, improved the world, and expanded opportunities for further discovery and application. But, in recent years the United States has been challenged by fiscal constraints, while other countries have quickened the pace of their investments (1).

Under these circumstances, it is important for the Nation to evaluate its scientific enterprise—and not just to determine how much we are prepared to invest. We must also understand the operation of our enterprise well enough to know how the basic and applied sciences can most effectively work together to create knowledge and to use that knowledge for the benefit of society through the applied sciences. I take that to be the ultimate goal of this hearing.

Such an evaluation of the scientific landscape is difficult because the terrain is complex and can be viewed in at least four dimensions. First, many approaches to science exist as defined disciplines, and a confluence of disciplines is often required for important discoveries (2); second, within many fields of inquiry, there is a spectrum of activities, ranging from basic studies of the fundamental principles of nature to more pragmatic

efforts to use basic knowledge to solve a wide range of societal problems, as originally described by Vannevar Bush (3); third, these many activities are supported by a variety of sources, including many governmental agencies, small and large companies, academic institutions, and private philanthropies; and, finally, financial support, especially from Federal science agencies, is provided through several kinds of mechanisms, including small and large grants to individuals, teams, and institutions for open-ended or targeted research or for training.

Balancing the elements in the landscape of science

Achieving an appropriate balance among these elements of the scientific enterprise is of obvious interest to this Subcommittee and to those, like today's panel members, who direct or have directed research on behalf of U.S. Government agencies, academic institutions, or private companies. Based on my own experience and observations as a leader of biomedical research in both the governmental and academic sectors, I would like to make four main points to help guide our discussion of the current dilemma:

- 1) For most major advances in medicine, several scientific disciplines have been essential (I will provide old, recent, and prospective examples below). Thus, the likelihood of more progress in the decades ahead requires diversified support and the encouragement of multi-disciplinary work.
- 2) When financial support is highly competitive, the choice of research projects veers towards the development of deliverable applications of existing knowledge and away from basic science, posing a serious risk to future productivity. This demands informed guidance from leaders in Government and industry to ensure the maintenance of a healthy environment for fundamental research.
- 3) Coordinated efforts among funding sources are desirable and possible but require the cooperation and attention of institutional leaders.
- 4) In my own domain of cancer research—and generally in medical research—several promising efforts are being made by the NCI and rest of the NIH to encourage inter-disciplinary “team” science, protect investigators pursuing fundamental studies, and work with funding partners (again, some specific examples will be mentioned below).

The importance of multiple disciplines to solve problems in medicine

From its earliest days, medical science has been dependent on the disciplines of physics and chemistry. The truth of this assertion is evident from any list of major

developments in medicine (4): microscopes (to identify infectious agents and cellular structures), X-ray machines (to reveal the living skeleton and delivery cancer therapy), radioisotopes (to track biological molecules and treat certain cancers), pharmacology (to determine the composition and fate of therapeutic drugs) and the EKG and EEG (to monitor the functional status of the heart and the brain through electrical activity).

More recently, major advances in the study of genes, proteins, and cells—from human beings and many other organisms—have revolutionized the study of normal and diseased human beings. This has been possible only because of crucial discoveries (*e.g.*, crystallography, mass spectroscopy, nuclear magnetic resonance, DNA sequencing methods and machines) that require physics, mathematics, engineering, and chemistry. Furthermore, the massive data sets now available from the use of these methods would neither exist nor be useful without the powerful tools provided by computational science. New devices for characterizing at one time many genes, many proteins or even many individual cells are the products of advances in physics and engineering—such as microfluidics, cryolithography, materials sciences, and nanotechnology.

Similarly, the ambitions of newly launched initiatives, such as the President's BRAIN project or therapeutics based on genetic signatures ("precision medicine"), will depend on principles of electrical circuitry, optogenetics, computation, mathematical modeling, and chemi-luminescence. In other words, the future of medicine, just like the past and present, will depend on the vibrancy of allied fields of science and technology and on the alertness of leaders of those fields to the possibilities for productive interaction.

Basic biological research is essential for future discoveries that will be applied to medicine

Most facets of medical research have been transformed over the past decade or two by the unveiling of genetic blueprints and the identification of the specific genetic and biochemical lesions that cause most human diseases. This means that even basic biomedical scientists without direct medical experience can now study human diseases and the means to prevent and treat them more effectively.

However, despite enormous increases in knowledge about mammalian biology, it is also clear that fundamental features of biological systems have yet to be discovered—sometimes because we have yet to develop the necessary experimental tools, sometimes because the right questions have yet to be asked and the right experiments have yet to be done.

This has been demonstrated dramatically over the past few years by the discovery of several unanticipated forms of RNA molecules that perform functions other than their well-known roles in the synthesis of proteins. Some very small RNA's interfere with the expression of one or more genes—functions that are biologically critical and experimentally transforming—and other longer RNA's have yet to be assigned a clear function. The need to study unusual organisms to probe the depth of biological complexity has also been illustrated by recent findings of enzymes that can permit rapid and efficient re-engineering of genes (*e.g.*, the TALEN and CRISPR systems) and of proteins that allow monitoring of gene expression and function with light of defined wavelengths (fluorescent proteins).

Furthermore, our understanding of the circuitry of biochemical signals that govern cell functions (such as cell growth, death, aging, metabolism, migration, information processing, and immune responses) are still in a primitive state. Unanticipated results and methods that can come only from unfettered basic research—involving biology, chemistry, physics, math, computational sciences and other disciplines—will be required to solve these problems and generate a new and completely unanticipated set of ideas from which practical applications can be developed.

Funders of research should aim for a balanced and synergistic portfolio

Many kinds of organizations support a wide array of research and development, so it is unrealistic to expect all components to attend to the needs of all disciplines or to the full spectrum of basic to applied research. For example, the financial demands placed on commercial entities prevent any extensive commitment to unfettered basic research, but those demands do intensify their interest in using new discoveries for development of useful products. Conversely, governmental science agencies, academic institutions, and some charities that support research have a mandate to invest in fundamental science with a long view—a long view that some unanticipated discoveries will be revolutionary in concept, establish positions of national and institutional leadership, and provide new foundations for product development by industry. Indeed, these are the ideas, articulated by Vannevar Bush nearly seventy years ago (3) that have been the basis for the past successes of American science.

Because the boundaries of research are more difficult to define than the extremes, there will inevitably be overlap in the ambitions of the entities that fund research, just as there are in the ambitions of those who perform it. But, the U.S. Government has a unique role in supporting basic research. At the same time, Government agencies, along with universities, private funders, and commercial entities, should be seeking ways to collaborate for at least three purposes: to learn where and how scarce resources are

being committed; to seek opportunities to engage in collaborative work; and to exchange information that may accelerate progress along the full spectrum of research and development.

NCI uses a variety of mechanisms to promote effective, multi-disciplinary research

Especially in fiscally challenging times, it is essential that the Government's science agencies maintain the public's trust by deploying their funds in accord with practices that have been productive in the past. The NCI, a component of the NIH, has benefited historically from a portfolio of funding mechanisms. These include the award of various kinds of grants and contracts to individuals, groups, and institutions to perform studies that range from investigator-initiated to agency-determined; the development of an intramural research program conducted by Government scientists in NCI laboratories; and the use of a Government-owned, contractor-operated cancer research laboratory in Frederick, Maryland.

We use these mechanisms to support basic, translational, and clinical work on a wide variety of cancer-related problems and to train scientists in several disciplines. Over the past few years, we have taken advantage of the flexible nature of the mechanisms to establish new programs that we believe are suited to the opportunities and stresses of our times. Some of these efforts are especially noteworthy in the context of today's discussion because of their inter-disciplinary or collaborative nature:

- The Cancer Genome Atlas (TCGA) project, now drawing to a close, has supported many hundreds of DNA sequencers, geneticists, bioinformatics experts, oncologists, and others to identify and compile an extensive set of characteristics about over twenty of the most common forms of human cancer. Now this information is being reviewed for general patterns, used for the pursuit of new diagnostics and therapeutics, and employed as a basis for more detailed studies of certain cancers.
- The Frederick National Laboratory for Cancer Research (FNLCR), itself modeled in part on the Department of Energy's national laboratories, has developed important core laboratories that serve the Nation's efforts in nanotechnology (the Nanotechnology Characterization Laboratory [NCL]), imaging, and other complex multi-disciplinary fields (the NCL is also part of the National Nanotechnology Initiative, a coordinated Federal activity spanning other NIH Institutes and 19 other Federal agencies).
- The FNLCR recently initiated a nationwide project to identify new strategies for attacking cancers driven by one of the three major genes in the RAS family (such

cancers constitute about a third of all human tumors). The RAS project has engaged a wide range of scientific expertise—in structural biology, protein chemistry, DOE-derived cell imaging methods, and computation—and investigators at many institutions.

- Both the intramural and the grant-making programs at the NCI have promoted the engagement of engineers, mathematicians, and physicists in cancer research. The intramural program has developed a partnership with physicists at the University of Maryland for collaborative projects. The extramural program has issued a request for applications to continue or create centers for the use of physical sciences in cancer research, and it issues grants and contracts for mathematicians to model cancerous cell behavior and for computational scientists to build cloud-based systems to store and analyze large data sets.
- To provide greater stability for NCI-funded investigators who have a record of high achievement and wish to engage in ambitious, long-term studies, the NCI has recently announced an Outstanding Investigator Award. We believe that these awards with encourage our best investigators to undertake risky work, particularly in the vulnerable fundamental sciences.
- To make “precision medicine” a reality in cancer treatment, the NCI is reorganizing the conduct of its clinical trials to include genetic characterization of each patient’s tumor and reference to large databases of clinical information to guide the choice of drugs to be tested. This requires extensive interaction with the Food and Drug Administration, the pharmaceutical industry, and patient advocacy groups, as well as collaboration among scientists and clinicians from several disciplines.
- The NCI’s Provocative Questions initiative was created a few years ago to bring imaginative scientists from several disciplines together to identify important questions about cancer that have yet to be adequately addressed. The most interesting questions are advertised by the NCI as topics for individual research projects and many grants have been awarded.

Reprise

Our complex and traditionally successful scientific enterprise now confronts expanded opportunities at a time of fiscal constraints and foreign challenges. Nurturing the health of many disciplines, preserving the Nation’s commitment to fundamental research, and coordinating the support of research from many funding sources will be essential to realize the potential of the Nation’s enterprise. The NCI is committed to those goals and has taken several steps to honor those commitments.

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Harold Varmus, M.D.
Director, National Cancer Institute

Harold Varmus, M.D., co-recipient of a Nobel Prize for studies of the genetic basis of cancer, was nominated by President Obama as Director of the National Cancer Institute on May 17, 2010. He began his tenure as NCI Director on July 12, 2010. He previously served as President and Chief Executive Officer of Memorial Sloan-Kettering Cancer Center (MSKCC) and as Director of the National Institutes of Health (NIH).

Much of Varmus' scientific work was conducted during 23 years as a faculty member at the University of California, San Francisco, Medical School, where he and Dr. J. Michael Bishop and their co-workers demonstrated the cellular origins of the oncogene of a chicken retrovirus. This discovery led to the isolation of many cellular genes that normally control growth and development and are frequently mutated in human cancer. For this work, Bishop and Varmus received many awards, including the 1989 Nobel Prize for Physiology or Medicine. Varmus is also widely recognized for his studies of the replication cycles of retroviruses and hepatitis B viruses, the functions of genes implicated in cancer, and the development of mouse models of human cancer (the focus of much of the work in his laboratory at MSKCC).

In 1993, Varmus was named by President Clinton to serve as the Director of NIH, a position he held until the end of 1999. During his tenure at NIH, he initiated many changes in the conduct of intramural and extramural research programs; recruited new leaders for most of the important positions at NIH; planned three major buildings on the NIH campus, including the Mark O. Hatfield Clinical Research Center ; and helped to initiate the five-year doubling of the NIH budget.

At MSKCC, Varmus emphasized opportunities to harness advances in the biological sciences to improve the care of patients with cancer. Under his leadership, the scientific programs were reorganized and enlarged; a new research building, the Mortimer B. Zuckerman Research Center, was constructed; and new graduate training programs were established in chemical biology and computational biology (as part of a new Tri-Institutional Research Program with Rockefeller University and Weill-Cornell Medical College) and in cancer biology (through MSKCC's first degree-awarding program in the Louis V. Gerstner, Jr. Graduate School of Biomedical Sciences).

In addition, he oversaw the construction of new clinical facilities (for pediatrics, pathology, urology, and surgery) and new centers for breast cancer treatment and imaging (the Evelyn H. Lauder Breast Center and the MSKCC Imaging Center); the founding of a hospital-based program in translational research (the Human Oncology and Pathogenesis Program); and the development of the Tri-Institutional Stem Cell Initiative and the Starr Cancer Consortium, involving five research institutions. To ensure that MSKCC was promoting high-quality cancer care for all citizens of New York and equal opportunities for its employees, he helped to found and oversee a new cancer clinic in central Harlem (the Ralph Lauren Center for Cancer Care and Prevention) and new programs for diversity and gender equity (the Office of Diversity Programs in Clinical Care, Research, and Training and the Women Faculty Affairs Program).

Varmus has authored over 300 scientific papers and five books, including an introduction to the genetic basis of cancer for a general audience and a memoir, *The Art and Politics of Science*, published in 2009. He has been an advisor to the Federal government, pharmaceutical and biotechnology firms, and many academic institutions, and was appointed by President Barack

Obama as co-chair of the President's Council of Advisors on Science and Technology (PCAST). He served on the World Health Organization's Commission on Macroeconomics and Health from 2000 to 2002; is a co-founder and Chairman of the Board of Directors of the Public Library of Science, a publisher of open-access journals in the biomedical sciences; chaired the Scientific Board of the Grand Challenges in Global Health at the Bill and Melinda Gates Foundation from 2003 to 2008 and now chairs the Foundation's Global Health Advisory Committee; and is involved in several initiatives to promote science in developing countries, including the Global Science Corps, through the Science Initiatives Group. He was also a member of the Funding Committee of the Empire State Stem Cell Board and serves as co-chair of the Institute of Medicine's committee on "The U.S. Commitment to Global Health." He has been a member of the U.S. National Academy of Sciences since 1984 and of the Institute of Medicine since 1991, and has received the National Medal of Science, the Vannevar Bush Award, and several honorary degrees and other prizes, in addition to the Nobel Prize.

A native of Freeport, Long Island, Varmus is the son of Dr. Frank Varmus, a general practitioner, and Beatrice Varmus, a psychiatric social worker. After graduating from Freeport High School, he majored in English literature at Amherst College and earned a master's degree in English at Harvard University. He is a graduate of Columbia University's College of Physicians and Surgeons, worked as a medical student in a hospital in India, and served on the medical house staff at Columbia-Presbyterian Medical Center. He began his scientific training as a Public Health Service officer at NIH, where he studied bacterial gene expression with Dr. Ira Pastan, and then trained as a post-doctoral fellow with Dr. Bishop at the University of California, San Francisco.

He is married to Constance Casey, a journalist and gardener, and has two sons, Jacob and Christopher.

Chairman BUCSHON. Thank you very much.
Now I recognize Dr. Tessier-Lavigne for five minutes.

**TESTIMONY OF DR. MARC TESSIER-LAVIGNE,
PRESIDENT AND CARSON FAMILY PROFESSOR,
LABORATORY OF BRAIN DEVELOPMENT AND REPAIR,
THE ROCKEFELLER UNIVERSITY**

Dr. TESSIER-LAVIGNE. Thank you, Chairman Bucshon, Chairman Smith, Mr. Lipinski, and other Members of the Subcommittee for the invitation to speak today about how best to harness public and private sector activities to drive critical breakthroughs for poorly treated diseases. As president of the Rockefeller University, I bring the perspective of the academic sector. Rockefeller is a graduate biomedical research university with a distinguished record. Over our 113-year history, our faculty has been honored with 24 Nobel Prizes in medicine and chemistry, more than any other institution in the world. As former Chief Scientific Officer at Genentech, a leading biotechnology company, I also bring a perspective from industry on how best to enable tomorrow's scientific and medical innovation.

I will start by noting that, despite great advances in health and life expectancy in past decades, as Chairman Bucshon noted, there is an urgent need for new therapies. Death rates from cancer remain stubbornly high, and chronic diseases, like Alzheimer's and diabetes, are on the rise. The suffering is immense, and the costs of care could bankrupt us.

The good news is that we are in a golden age of disease research, thanks to technological advances like genome sequencing. If we make the necessary investments, we can understand why tumors spread, why nerve cells die in Alzheimer's disease, and the secrets of our immune system. But gaining this knowledge is only half the battle. Translating discoveries into new therapies is a complex process with substantial attrition.

For every 24 drug discovery projects initiated based on basic science discoveries, only nine candidate drugs eventually enter human clinical trials, only one of which will make it all the way to approval to help patients in the marketplace. Twenty-four down to one. This process takes, on average, 10 to 15 years, and more than a billion dollars for every approved drug, a huge and lengthy investment.

Complex as it is, this process is remarkably successful thanks to four major groups of stakeholders working closely together. The first are biomedical scientists in academia and government, who create new knowledge with federal support. They explore the inner workings of cells and organs in health and in disease, relying in important ways on instruments, tools, and methodologies provided by the harder sciences, physics, chemistry, math, and computer science, as has already been noted.

Second are the large biopharmaceutical companies who lead the complex drug development process based on that knowledge. Two additional stakeholders, disease foundations and small biotechnology companies, facilitate progression at the interface of the first two. This ecosystem plays to the strength of each participant. Academia provides an unfettered environment where researchers

can best explore scientific leads to break open new fields, whereas companies, with their tightly defined structure, are better suited to mounting the directed studies needed for drug discovery and development. And only the federal government has the resources and time horizon to invest in basic research that may not see a return for many decades. Companies already stretched thin by the duration and expense of drug development do not.

Historically, this ecosystem has worked successfully, so much so that approximately half of all new drugs today are discovered in the United States. This investment has benefitted patients, saved trillions in overall healthcare costs, and boosted the economy enormously, generating high paying jobs and increased economic activity, and it has stimulated massive biotech and pharmaceutical investments in the U.S.

How, then, should we maximize this vital drug discovery and development ecosystem, and what risks do we face? The logic of the biopharmaceutical sector is simple. Companies locate their R&D operations near the sites of scientific innovation in academia to tap into the best scientists and a highly skilled work force. And companies will make significant, even multibillion dollar, investments in breakthrough therapies on two conditions: if basic scientists provide sufficient understanding of disease processes to justify the bets, and if they see a path to getting an adequate return on their investment.

The government's role in supporting a vibrant basic research sector is, therefore, essential to understanding poorly treated diseases. If the academic sector generates the knowledge, the private sector will then rush in to apply it. Programs like the NIH sponsored BRAIN initiative, and its accelerating medicines partnership with industry can help focus on areas of high unmet medical need, like psychiatric disease, and facilitate translation of discoveries into drugs.

Conversely, reductions in federal support for science over the past decade have weakened our ecosystem, with promising young investigators turning away from the field to pursue more stable careers, and scientists relocating to countries where research funding is less challenging. If this trend continues, we will see industry relocate to emerging sites of innovation abroad. Countries in Asia, like China and South Korea, as well as in Europe, are investing to become new epicenters of biomedicine, and they are succeeding.

Beyond supporting the research sector, government must also continue to address important structural issues to ensure our country is attractive to private sector investment. Key requirements include sufficient protections of intellectual property, tax policies that favor R&D investments, and support of STEM education to provide a highly trained work force.

In conclusion, we now find ourselves at a time of huge medical need, but also enormous scientific and economic opportunity. To retain its preeminence in this golden age of biomedicine, the United States must pursue the necessary investments and structural policies. Thank you for your attention.

[The prepared statement of Dr. Tessier-Lavigne follows:]

Congress of the United States
U.S. House of Representatives
Committee on Science, Space, and Technology
Subcommittee on Research and Technology

**“Policies to Spur Innovative Medical Breakthroughs
from Laboratories to Patients”**

Written Testimony
of
Dr. Marc Tessier-Lavigne

Rayburn House Office Building
Room 2318
Thursday, July 17, 2014
9:00 – 11:00 a.m.

Thank you, Chairman Bucshon, and members of the subcommittee, for the invitation to speak to you today about a critical issue facing the nation: how best to stimulate public and private sector biomedical research and development activities to drive medical breakthroughs for poorly treated diseases.

As president of The Rockefeller University, I bring the perspective of the academic research sector. Rockefeller is a research institution in New York City home to 75 laboratories and about 1,200 scientists working on advancing knowledge of biological processes in most fields of biomedicine, from brain science to cancer biology to metabolic disease.

Rockefeller has been extraordinarily successful at making discoveries that have advanced the fight against diseases such as cancer, HIV/AIDS, Alzheimer's disease and stroke. One measure of our success is that our faculty have been honored with 24 Nobel Prizes in medicine and chemistry over our 113-year history, more than any other institution in the world.

As former chief scientific officer at Genentech, a leading biotechnology company, I also bring a perspective from industry on how best to enable tomorrow's scientific and medical breakthroughs.

Overview

In my presentation today, I will address the following points. First, despite great health gains over past decades, the burden of disease continues to grow. However, if we invest adequately in basic biomedical research, we can create the knowledge that will in turn trigger private-sector investment to develop therapies to conquer such diseases. But industry will concentrate its investment in the United States only if we remain research leaders and maintain adequate incentives for R&D investment. I will take these points in turn.

The need and opportunity for new therapies

Let's start by celebrating the great advances in health we've enjoyed in past decades. Mortality from heart disease and stroke has been cut in half in 40 years. HIV/AIDS has been transformed into a disease that's manageable without hospitalization. Life expectancy in the United States has increased by 10 years since 1950. [1]

But we must also recognize the urgent need for new therapies. Death rates from cancer remain stubbornly high. Infectious diseases are becoming resistant to our arsenal of antibiotics. Chronic diseases like Alzheimer's and diabetes are on the rise.

The suffering is immense, and the costs of care could bankrupt us. Just one example is that without effective therapy, the cost for Alzheimer's is estimated to grow to \$1.2 trillion a year by 2050 in the U.S. because of the aging of the population. [2]

The good news is that we're in a golden age of disease research, thanks to sequencing of the human genome and development of other powerful technologies. If we make the necessary investments, we can understand why tumors spread, we can learn why nerve cells die in Alzheimer's disease, and we can unlock the secrets of our immune system.

And that knowledge is needed for us to conquer cancer, defeat dementia, and develop vaccines for HIV. Our lack of understanding of what goes wrong in the brain in psychiatric diseases

explains why drug discovery efforts for these devastating conditions have ground to a halt. The equation is simple: no knowledge...no treatments...no cures.

A vibrant public-private partnership drives development of therapies

So how can we best enable the generation and application of scientific knowledge to bring new medicines to patients and the marketplace? The answer to this question requires an understanding of the drug discovery process and stakeholders.

There are two facts about the process that I need to highlight at the outset.

The first is the inherently complex nature of the drug discovery pyramid. For every drug approved by the FDA at the top of the pyramid, the foundation consists of dozens of insights into diseases generated over a period of decades, largely through federal funding of basic, knowledge-driven research. In between, for every 24 drug discovery projects initiated based on those fundamental discoveries, only nine candidate drugs eventually enter human clinical trials, only one of which will make it all the way to approval.

The second fact is that progressing from 24 drug-discovery projects to one FDA approved drug that can help patients takes on average 10-15 years and more than \$1.2 billion – a huge and lengthy investment. [3]

Despite these challenges, the ecosystem works thanks to four major groups of stakeholders that coordinate their work in the stepwise process of biomedical discovery and drug development. Their combined efforts have resulted in approximately half of all new drugs today being discovered in the United States.

At the foundation are academic and governmental institutions engaged in fundamental research. Scientists at Rockefeller and thousands of others embedded in academic research institutions across the country conduct the bulk of the critically important work that underlies the drug development process. This knowledge-driven research is funded by the federal government, through competitive grants, and to a lesser extent by philanthropic interests.

Biologists at this stage investigate how the body works in both health and in disease. They strive to understand what makes normal cells turn cancerous, how brain circuits normally function but sometimes malfunction in neurological or psychiatric diseases, and what causes the immune system to mistakenly attack the body's own tissues.

These discoveries also rely in essential ways on advances in instrumentation, tools, and methodologies generated by the harder sciences: physics, chemistry, math and computer science. In recent years, such technological progress has driven an extraordinary acceleration in biomedical discovery. As one example, the cost of sequencing an organism's genome has dropped to a fraction of what it was during the Human Genome Project, both in terms of cost and the time needed to perform the task. Today, many of our laboratories have the ability to sequence an entire human genome in days or weeks instead of the decade and more it once took, and for only a few thousand dollars instead of the roughly \$2.7 billion that was needed initially. [4]

While academic research labs generate most of the biological insights into disease, the 10- to 15-year odyssey of making and testing candidate drugs is mostly the work of pharmaceutical

companies. They determine whether potentially disease-causing processes identified by basic scientists can be blocked or corrected. Can a compound be created that prevents, say, a cancerous cell from multiplying? If such a compound is found, then it must be thoroughly tested in the laboratory, in animals, and eventually in humans. This work is typically done on a scale not possible in academic labs.

Two additional stakeholders, disease foundations and small biotechnology companies, help grease the wheels of this translational process. They function at the interface of the first two, helping sift through mechanisms discovered in academic laboratories to identify the most promising ones. They even sometimes initiate generation and testing of drugs, but typically partner at that stage with larger firms, which have the infrastructure and financial resources needed to drive candidate drugs through human clinical trials.

This division of labor has evolved in response to two main factors, one financial and the other cultural.

Financially, the huge costs and timelines of drug development mean that pharmaceutical firms already manage substantial risks to remain financially viable while making and testing drugs. They do not have any additional resources to fund the fundamental inquiries into disease biology that are needed as the foundation for drug discovery. Small biotech firms have even fewer resources. While disease foundations and other philanthropies provide an important assist, ultimately only the federal government has the resources and the time horizon to invest in basic research that may not see any return, at least in terms of yielding viable drug targets, for a decade or more.

Culturally, academia provides the right kind of unfettered environment where the most innovative scientists have the best chance of exploring new scientific leads to break open new fields. Companies, on the other hand, are better suited to conducting the directed studies needed for drug discovery and drug development because of the massive infrastructure and hierarchical teams that are needed.

Although there are exceptions – some biotech companies do engage in basic research, for example, and academic institutions do occasionally test drugs – the centers of gravity I have just described have been in place for decades because they play to the strengths of each stakeholder.

To give an example of the differences in emphasis, at Genentech, one of the largest biotech companies in the world and one that invests more heavily in basic research than most or all of its competitors, we could only afford about 100 postdoctoral fellows working in basic science when I was there. Postdocs are the workhorses of basic research. By contrast, at Rockefeller, a tiny academic institution by most measures, we have roughly 400 in our laboratories at any given time.

Historically, this drug discovery and development ecosystem works. Thanks in large part to the nation's long-term investment in basic biomedical science, as well as in physics, chemistry, engineering, computer science and other disciplines that have created the advanced instrumentation and data-processing tools biologists rely on, the United States has become the undisputed leader in pharmaceutical breakthroughs.

Benefits to patients and the nation of the bioscience enterprise

Most important, this investment has benefited patients, who have more treatment options than ever before and are enjoying longer and healthier lives.

It has benefited the nation, with new and more effective drug therapies responsible for saving trillions of dollars in overall health care costs. The return on the investment is evident when you consider that the annual spend per citizen per year on the NIH is only \$100, a minuscule amount compared to the \$8,000 per citizen per year spent on health care.

The biomedical investment also boosts the economy enormously, generating high-paying jobs and increased economic activity.

And it has stimulated private investment in this vital economic sector, luring biotech and pharmaceutical investments in the United States. By one assessment, every dollar of public investment in this area leads to an additional \$8.38 of private R&D investment.

How can we stimulate private investment and a focus on breakthrough therapies?

The industrial logic of the biopharmaceutical sector is simple. Companies locate their R&D operations near the sites of scientific innovation in academia, both to tap into the best scientists and their discoveries, and to access the highly skilled workforce trained in their laboratories. And all that is needed to drive them to make significant – even multibillion dollar – investments in breakthrough therapies are two conditions: that there is enough knowledge about disease processes to justify the bets, and that they see a path to getting an adequate return on their investment.

The government's role in supporting a vibrant academic research sector through sufficient NIH and NSF funding is therefore essential. This funding generates the necessary knowledge and attracts industry and private-sector investment. In this ecosystem, there is no substitute for the role of federal funding of basic science.

Basic research funding enables the best minds to tackle the most important problems. It can also help direct them to important areas of need. The NIH-sponsored BRAIN initiative is an example of a strategic initiative that builds on recent scientific breakthroughs to break open our understanding of brain diseases. If the academic sector generates the knowledge, the private sector will rush in to apply it.

Conversely, we have seen that reductions in federal support for science over the past decade have triggered a crisis in the biomedical research enterprise, with many scientists spending more time applying for grants than doing research, and with highly trained young investigators turning away from the field to pursue more stable careers.

If this trend continues, not only will we undermine our research enterprise, we will also see industry relocate to the emerging sites of innovation abroad. While U.S. public investment in science erodes, countries in Asia like China, India, South Korea, Taiwan and Singapore, as well as a number of countries in Europe, are multiplying their investments and striving to become new epicenters of biomedicine. And they are succeeding. Already, they are attracting top talent as, increasingly, individual scientists choose to move to countries where securing funding for their work is less difficult.

Beyond supporting the research sector, government must also address also important structural impediments that make our country less attractive to private sector investment.

The key requirements have been well documented by the major trade organizations. They include sufficient protections of intellectual property, tax policies that are competitive with other countries – including a permanent tax credit for research and development – free trade agreements, fair pricing policies, and investments in STEM education and immigration policies that enable companies to draw on both local talent and the best scientists from abroad. [5]

In conclusion, we now find ourselves at a time of huge medical need—but also enormous scientific opportunity. And yet, we're pulling back. Our basic science investment as a percentage of GDP is at its lowest in 40 years. [6]

The bottom line is one that bears repeating. Adequate federal support of basic science is the single most important factor in ensuring the productivity of the U.S. biomedical sector. It provides the foundation of an entire industry and directly spawns the new knowledge from which medical breakthroughs follow. No knowledge...no therapies...no cures.

Thank you for your attention and your continued efforts to support the biomedical enterprise for the benefit of our citizens and the nation.

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Marc Tessier-Lavigne

Dr. Tessier-Lavigne is president of The Rockefeller University, where he is also Carson Family Professor and Head of the Laboratory of Brain Development and Repair. He is a pioneer in the study of molecular signals that direct formation of neural circuits in the brain during embryonic development. He also studies nerve cell responses to injury and the mechanisms underlying nerve cell death in neurodegenerative diseases. Previously, he served as chief scientific officer at Genentech, a leading biotechnology company. He obtained undergraduate degrees from McGill and Oxford Universities and a Ph.D. from University College London (UCL), and was a postdoctoral fellow at UCL and Columbia University. Prior to joining Genentech, he held faculty positions at the University of California, San Francisco and at Stanford University, where he was the Susan B. Ford Professor and an Investigator with the Howard Hughes Medical Institute. A Rhodes Scholar, Dr. Tessier-Lavigne is the recipient of numerous awards and honors, including being elected a member of the National Academy of Sciences and its Institute of Medicine. He also serves as scientific advisor or board member for several not-for-profit organizations and biopharmaceutical companies.

Chairman BUCSHON. Thank you very much.
I now recognize Dr. Keasling for five minutes to present his testimony.

**TESTIMONY OF DR. JAY KEASLING,
HUBBARD HOWE JR. DISTINGUISHED PROFESSOR
OF BIOCHEMICAL ENGINEERING,
UNIVERSITY OF CALIFORNIA, BERKELEY;
PROFESSOR, DEPARTMENT OF CHEMICAL &
BIOMOLECULAR ENGINEERING,
UNIVERSITY OF CALIFORNIA, BERKELEY;
PROFESSOR DEPARTMENT OF BIOENGINEERING,
UNIVERSITY OF CALIFORNIA, BERKELEY;
DIRECTOR, SYNTHETIC BIOLOGY ENGINEERING RESEARCH
CENTER**

Dr. KEASLING. Chairman Bucshon, and distinguished Members of the Committee, I thank you for the opportunity to testify at this important hearing, and for your strong and sustained support for science and technology. Today I would like to begin to tell a story of how we engineered a microbial production process for a much needed drug to combat a deadly disease that affects millions of children around the world, and how repurposing that same process allows us to meet needs not only for health, but also for energy, and the environment.

There are approximately 250 million cases of malaria every year, causing nearly a million deaths annually. Most of the victims are children under the age of five. A child dies of malaria every minute. Conventional quinine-based drugs are no longer effective. While plant derived artemisinin combination therapies are highly successful, for many malaria victims, they are simply too expensive.

To bring down the cost of the therapy and stabilize the supply, we engineered a microbe, a yeast, to produce a precursor chemical to the drug. To do this, we transferred genes responsible for making the drug from the plant to a microorganism. The process of producing artemisinin is akin to brewing beer. Rather than spitting out ethanol, the microbes spit out artemisinin. The microbe consumes that sugar, and produces the drug from that sugar.

We licensed this microbial production process to Sanofi-Aventis, who scaled the process to industrial levels. This year, Sanofi-Aventis produced 70 million doses of artemisinin, and is on track to produce 100 to 150 million every year for the next few years, roughly half the world's needs. We predict that the drug produced by this process could save a large fraction of the annual one million children that die of malaria.

Begun in 2004, the artemisinin project was supported by a \$42 million grant from the Bill and Melinda Gates Foundation, and took roughly 150 person years' worth of work to complete the project. We were able to complete the project largely due to readily available, well characterized biological components, a significant point that I will return to shortly.

The artemisinin story demonstrates the significant medical benefits of engineering biology, but also reveals how these benefits ex-

tend to chemical manufacturing. Unfortunately, engineering biology is still time consuming, unpredictable, and expensive, and many urgent challenges in health, and energy, and the environment remain needlessly unresolved. Efforts to—aimed at making biology easier to engineer have come to be known as synthetic biology.

As was the case with the development of synthetic artemisinin, synthetic biology represents a convergence in the advances in chemistry, biology, computer science, and engineering. Experts in the fields work together to create reusable methods for increasing the speed, scale, and precision with which we engineer biological systems. In essence, this work can be thought of as the development of biological based toolkits that enable improved products across many industries, including medicine and health.

About ten years ago, around the start of the artemisinin effort, several colleagues and I set out to develop these more generalized approaches to making biology easier to engineer. We believed that we could engineer microbes to produce virtually any important chemical from sugar, yet there was a severe lack of publicly accessible tools for building biological processes and products, so we went out to the National Science Foundation, proposed a center dedicated to building these tools for the research community. In response, NSF granted us the Synthetic Biology Engineering Research Center, a ten year multi-institutional research project designed to lay the foundations for engineering biology.

Now, eight years later, SynBERC has produced a broad range of toolkits that are being developed in the fields of energy, agriculture, health, and security, and offer an array of economic benefits. When SynBERC was established in 2006, it was the nation's single largest research investment in synthetic biology.

Eight years later, this, and other federal funding, have catalyzed the growth of academic research centers around the country, the production of many synthetic biology enabled chemicals in the private sector, five startup companies from SynBERC itself, and a robust private/public consortium that helps guide the research from lab bench to bedside.

The U.S. model has been so successful that other countries, particularly China and the U.K. are developing aggressive, nationally coordinated research programs in an effort to surpass the U.S. to become the global leaders in biological engineering. These investments in synthetic biology are already making their mark on national economies. By some estimates, domestic revenues from biologically engineered systems was thought to account for more than 2.5 percent of U.S. GDP in 2012, with a growth rate of 10 percent.

The U.S. has been a leader in this field because of early and focused federal investment, but we now face stiff competition from overseas, and uncertainty in our pre-competitive investments here at home. I believe that now is the time for federal government to work with academic and industrial researchers to launch a national initiative in engineering biology, to establish new research directions, technology goals, and improve inter-agency coordination. I thank you for your time.

[The prepared statement of Dr. Keasling follows:]

**Testimony
Before the
Subcommittee on Research and Technology
Committee on Science, Space, and Technology
United States House of Representatives**

**Statement of
Jay D Keasling, PhD
Professor, University of California, Berkeley
Senior Faculty Scientist, Lawrence Berkeley National Laboratory**

Chairman Bucshon (R-IN) and distinguished members of the Committee, thank you for the opportunity to testify at this important hearing, and for your strong and sustained support for science and technology development. My name is Jay Keasling, and I am a Professor of Chemical and Biomolecular Engineering and of Bioengineering at the University of California, Berkeley and Senior Faculty Scientist at the Lawrence Berkeley National Laboratory. I serve as the Director of the National Science Foundation-funded Synthetic Biology Engineering Research Center and CEO of the Department of Energy-funded Joint BioEnergy Institute.

Today, I would like to tell the story of how we engineered a microbial production process for a much-needed drug to combat a deadly disease that affects millions around the world, and how repurposing this same process allows us to meet needs not only for health, but also for energy and the environment. In doing so, I will argue that sustained federal investments that encourage the growth of synthetic biology, an emerging, multi-disciplinary field, is a critical component of both continued U.S. economic prosperity and security with enormous societal benefits.

There are approximately 300 million cases of malaria at any one time, approximately one million people die from the disease every year, and 90 percent of those are children under the age of five. Conventional quinine-based drugs are no longer effective, and while plant-derived artemisinin combination therapies are highly successful, for many malaria victims, they are also cost prohibitive.

To bring down the cost of the therapy and stabilize the supply, we engineered a microorganism to produce a precursor chemical to the drug. To do this, we transferred the genes responsible for making the drug from the plant to a microorganism. This process of producing artemisinin is akin to brewing beer. The microorganism consumes a sugar and secretes a precursor to artemisinin rather than alcohol, which the yeast would produce naturally from sugar.

We have licensed this microbial production process to Sanofi-Aventis, who has scaled the process to industrial levels. This year, Sanofi-Aventis produced 70 million doses of artemisinin and is on track to produce 100-150 million next year, roughly half of the world's need. We predict that the drug produced by this engineered organism could save a large fraction of annual one million child victims of malaria.

Begun in 2004, the artemisinin project was supported by \$25 million from the Bill and Melinda Gates Foundation and roughly 150 person-years of work. We were able to complete the project in that brief time largely due to ready access to well-characterized biological components, a significant point that I will return to shortly.

The artemisinin story demonstrates the significant medical benefits of engineering biology, but also reveals how these benefits extend to chemical manufacturing as well. For example, 1,3-propanediol is an important industrial chemical used to make carpets, textiles, cosmetics, personal care and home cleaning products. In 1993, Dupont embarked on a major research effort to engineer the microbe *E. coli* to produce 1,3-PDO, in order to replace the petroleum-based process used to make the chemical. It took 15 years and \$130 million in research and development for Dupont to make a bio-based, sustainable process that consumes 40% less energy and produces 20% less greenhouse gases.

Artemisinin and propanediol are just two examples of how engineering biology can create a more cost effective and sustainable manufacturing process, and even save lives. Unfortunately, engineering biology is still time-consuming, unpredictable and expensive and many urgent challenges in health, energy and the environment remain needlessly unsolved. Today, most of our bulk chemicals and materials are derived in whole or in part from petroleum. What if we could take plants, CO₂ and sunlight and output useful, sustainable substitutes for petroleum-derived products? What if we could engineer biological systems to generate medical cures like artemisinin and green chemicals like bio-PDO in months rather than years?

Efforts aimed at making biology easier to engineer have come to be known as “synthetic biology.” As was the case with the development of synthetic artemisinin, synthetic biology represents a convergence of advances in chemistry, biology, computer science, and engineering. Experts in these fields work together to create reusable methods for increasing the speed, scale, and precision with which we engineer biological systems. In a sense, this work can be thought of as the development of a biology-based “toolkit” that enables improved products across many industries, including medicine and health.

About ten years ago, around the start of the artemisinin efforts, several colleagues and I set out to develop these more generalizable approaches to making biology easier to engineer. We believed we could engineer microorganisms to produce virtually any important chemical from sugar. Yet there was a severe lack of publicly accessible tools for building biological processes and products. So we went to the National Science Foundation and proposed a center dedicated to building such tools for the research community. In response, the NSF established the Synthetic Biology Engineering Research Center. Synberc is a ten-year multi-institutional research project designed to help lay the foundations for the emerging field of synthetic biology. Synberc’s investigators come from across the US, and from a range of disciplines, including chemistry, biology, computer science, engineering and the social sciences. Now eight years since its founding, Synberc has produced a broad range of “toolkits” that are being deployed in the fields of energy, agriculture, health and security, and offer an array of economic and societal benefits.

When Synberc was established in 2006, it was the nation's single largest research investment in synthetic biology. Eight years later, this and other federal funding have catalyzed the growth of academic research centers across the country, the production of many synthetic biology-enabled chemicals in the private sector, five start-up companies from Synberc itself, and a robust private-public consortium that helps guide research from the lab bench to the bedside. This U.S. model has been so successful that other countries – particularly China and the U.K. – are developing aggressive, nationally coordinated research programs in an effort to surpass the U.S. to become the global leaders in biological engineering.

The U.S. has been a leader in this field because of early and focused federal investment, but we now face stiff competition from overseas and uncertainty in the future of our pre-competitive investments here at home. I believe that now is the time for the federal government to work with academic and industrial researchers to launch a national initiative in engineering biology to establish new research directions and technology goals, improve interagency coordination and planning processes, drive technology transfer, and help ensure optimal returns on the Federal investment. Here are specific areas where the Federal government can play a crucial role in advancing engineering biology for the greatest public benefit:

- Sustained **Federal investment in foundational tools and research** would expand the biological toolkit to accelerate processes in health and medicine, as well as in other fields, and make entirely new applications possible;
- Interagency coordination would enable a **shared research agenda and vision** for achieving outcomes consistent with public values and priorities;
- Promotion of **industry-academic-government collaboration** is needed to align strategic research aims, spur economic development, promote commercialization of academic research, leverage private investment and encourage new start-up ventures;
- **Policy coordination and regulatory research and development capacity** is needed to address potential economic, security, safety, and environmental effects of engineering biology, establish regulatory jurisdiction, reduce regulatory uncertainty, and address ethical, legal and social concerns;
- **Education and leadership development** is needed to create tomorrow's practitioners, educators, legislators, and regulators, and a workforce that is diverse in socioeconomic background, discipline, and thought;
- Development of **public infrastructure**, such as libraries of genetic information and materials, core facilities for biological manufacturing, and practices for managing intellectual property, and establishing engineering standards, will provide the pre-competitive platform for innovators to thrive; and
- **Public engagement at the national level** is needed to educate, inform, learn, and engage in a robust debate about how to create science that is toward in the greatest public interest, and carried out in a transparent and just manner

In short, we need a national infrastructure that continues to support collaboration, constructive competition, and the production of tools and knowledge needed to responsibly and productively harness the capabilities of engineering biology. *The federal government's support for foundational tools and technologies are the real key to U.S. competitiveness.*

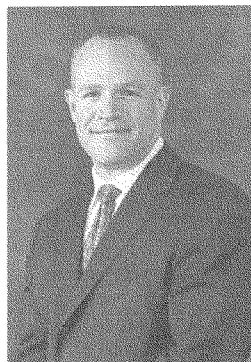
I have focused on health-related applications and synthetic chemical production today, but the potential benefits of synthetic biology are by no means limited to those sectors. Agriculture, materials, energy, and bioremediation all stand to benefit greatly from this advanced engineering and manufacturing platform. Indeed, the microorganism that we engineered to produce artemisinin is also being used to produce cosmetics and biofuels.

Just as the information age transformed life in the 20th century, so too the engineering of biology is poised to bring tremendous changes to society in the 21st century. And we will be able to do it more quickly, more cost-effectively, and more precisely than ever before. But we must act quickly to put a national initiative in play; the role of the U.S. in the bioeconomy that results from the tools of synthetic biology will be determined by the actions of the federal government in the next five years.

Thank you for giving me the opportunity to talk to you about the remarkable potential of biological engineering, and the important role that it has to play in our nation's research and innovation enterprise. We cannot realize this potential, however, unless together we pursue a national initiative in engineering biology. Your actions and the support of Congress will determine whether the efforts described here today are ultimately successful. We stand ready to assist in any way we can as you explore and learn more about this exciting, game-changing research area.

Jay D. Keasling Biography

Jay D. Keasling is the Hubbard Howe, Jr. Distinguished Professor of Chemical & Biomolecular Engineering and of Bioengineering at the University of California, Berkeley. He is the Director of the Synthetic Biology Engineering Research Center (Synberc), Associate Laboratory Director for Biosciences at the Lawrence Berkeley National Laboratory, and Chief Executive Officer of the Joint BioEnergy Institute. In addition, Keasling has founded or co-founded four companies, including Amyris, a leading firm in the development of renewable fuels and chemicals.



Keasling is one of the foremost authorities in the field of synthetic biology research, and in particular on metabolic engineering. His work has focused on engineering microorganisms for the environmentally friendly synthesis of small molecules or degradation of environmental contaminants. He led the breakthrough research in which bacteria and yeast were engineered to perform most of the chemistry needed to make artemisinin, the most powerful anti-malaria drug in use today. In 2004, the Bill and Melinda Gates Foundation awarded a \$42.6 million grant to further develop the technology, which is now nearing commercialization. For this research, Keasling received the 2009 Biotech Humanitarian Award from the Biotechnology Industry Organization. Keasling is now applying his synthetic biology techniques towards the production of advanced carbon-neutral biofuels that can replace gasoline on a gallon-for-gallon basis.

Keasling grew up on his family's corn and soybean farm in Harvard, Nebraska, then earned his bachelor's degree from the University of Nebraska, and his graduate degrees in chemical engineering from the University of Michigan. He is the recipient of the American Institute of Chemical Engineers Professional Progress Award (2007) and Scientist of the Year, Discovery Magazine (2006). In 2006, he was cited by Newsweek as one of the country's 10 most esteemed biologists. He is a Fellow of the American Academy for Microbiology (2007) and the American Institute of Medical and Biological Engineering (2000). In 2010 he was elected to the prestigious National Academy of Engineering.

Chairman BUCSHON. Thank you very much.
I now recognize Dr. Venter for five minutes to present his testimony.

**TESTIMONY OF DR. CRAIG VENTER,
FOUNDER, CHAIRMAN, AND CHIEF EXECUTIVE OFFICER,
J. CRAIG VENTER INSTITUTE, SYNTHETIC GENOMICS, INC.,
AND HUMAN LONGEVITY, INC.**

Dr. VENTER. Chairman Bucshon, distinguished Committee Members, thank you for the invitation to be here today. I represent a not-for-profit independent research institute, the J. Craig Venter Institute, and two biotech companies, Synthetic Genomics, and Human Longevity, Inc. We have a combination of funding from the private sector, from donations, from DOE, from DARPA, from NASA, from NSF, NIH, BARDA, and a range of interactions that range from 100 percent privately funded to 100 percent publicly funded.

This is a very exciting time in science, as you have heard from my colleagues. We now have the ability to interchange the genetic code and the digital code in the computer. We can read the genetic code, put the data in the computer, and now we have shown, as my colleague Jay Keasling has discussed, we can go the other way, and actually write the genetic code. And, four years ago, we announced the creation of the first synthetic organism, completely writing the chemical genetic code.

This is having implications in lots of areas. We have had a great collaboration with BARDA and Novartis for making the first synthetic vaccine against flu. When H7N9 flu broke out in China, a team in China sequenced the genome from a patient, posted it on the Internet. We downloaded it, and within a few hours synthesized the H7N9 virus. That was immediately started in development for a vaccine. BARDA has now stockpiled a substantial amount of the H7N9 vaccine before the first case has appeared in the U.S. It is the first time in history where the U.S. is ready for a deadly pandemic before the first case has reached this country.

We can send vaccines through the Internet. Biological information now moves around the world digitally. It is not a matter of sending DNA in clones. We are using this in lots of different ways. We had recently announced, at Synthetic Genomics, a collaboration with United Therapeutics to re-engineer the pig genome, humanizing the pig genome to allow organ transplantation of hearts, kidneys, and lungs into humans to meet a huge medical need of lack of organ transplants. This comes from all these new tools for writing and editing the genome. You have heard from Jay Keasling how this can be done to create chemicals. We have engineered a synthetic genomic algae to produce large amounts of Omega-3 fatty acids that ADM is taking into extremely large scale production.

The ultimate application of all this is in medicine. We have recently announced that Human Longevity formed the largest human DNA sequencing facility in the world. We are scaling up from 15 years ago, when we sequenced one genome over nine months for roughly \$100 million to doing 100,000 genomes a year, hopefully within 18 months, with the goal to have one million human

genomes by 2020 in a database to allow this data driven practice of medicine.

This is a very exciting era, but it is a challenge, as you have heard from my colleagues, with the changes in government funding, and the competition from overseas, as Dr. Keasling talked about. In this same field, the Chinese government supports their industry to the tune of billions of dollars, versus competition with industry. These challenges are important, exciting. Also we deal with the public policy issue. Bob Friedman, my colleague, is head of policy at the Venter Institute. We have been asking ethical questions before anybody else. We have driven them, and the latest iteration of this was when we announced the first synthetic cell. The Obama Administration asked their new bioethics commission to take this on as their number one challenge.

These are exciting times, they are challenging times, but this science has a chance to revolutionize medicine, and perhaps be a new industrial revolution. I am pleased to take any questions. Thank you very much.

[The prepared statement of Dr. Venter follows:]

PREPARED STATEMENT OF

**J. CRAIG VENTER, PH.D.
CHIEF EXECUTIVE OFFICER, J. CRAIG VENTER INSTITUTE,
SYNTHETIC GENOMICS, INC., AND
HUMAN LONGEVITY, INC.**

**BEFORE THE
U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
SUBCOMMITTEE ON RESEARCH AND TECHNOLOGY
July 17, 2014**

Mr. Chairman and Committee members, I welcome the opportunity to testify before you today. I am J. Craig Venter, Ph.D., Founder, Chairman, and Chief Executive Officer of the J. Craig Venter Institute (JCVI). The JCVI is a not-for-profit research institute in La Jolla, CA and Rockville, MD dedicated to the advancement of the science of genomics; the understanding of its implications for society; and communication of those results to the scientific community, the public, and policymakers. The JCVI is home to approximately 250 scientists and staff with expertise spanning microbiology to human biology, genomics, bioinformatics/informatics, information technology, high-throughput DNA sequencing, policy research, and public education in science. The JCVI is a 501 (c) (3) organization.

I am a Co-Founder and Chief Executive Officer of Synthetic Genomics Incorporated (SGI), a privately held company located in La Jolla, California dedicated to commercializing genomic-driven solutions to address global needs such as new sources of energy, new food and nutritional products, and next generation vaccines.

Finally, I recently co-founded and am Chief Executive Officer of Human Longevity, Inc. (HLI), a genomics and cell therapy-based company focused on extending the healthy, high performance human lifespan. HLI's mission is to identify the therapeutically targetable mechanisms responsible for age-related human biological decline and to develop and apply innovative solutions to interrupt or block those processes, thereby meaningfully extending human lifespan.

In your letter of invitation to testify today, you asked me to address three questions:

- 1) What are the promises and limitations of synthetic biology, especially in advancing progress and understanding of biomedical problems?
- 2) How should federal science agencies approach funding of important biomedical science research?

- 3) How important are non-government research efforts in developing innovative treatments and how do these efforts complement or compete with government investment?

What are the promises and limitations of synthetic biology, especially in advancing progress and understanding of biomedical problems? What legal and ethical issues in synthetic biology must be addressed at this time?

Genetic engineering which has been the engineering of one or a few genes in organisms to create a new trait or effect from that organism has been transformed in recent years into the field of “synthetic biology” with the ability to rewrite multiple genes and pathways or even to create entire chromosomes and genomes from scratch.

These breakthroughs have significantly expanded the tool kit available to scientists and engineers, providing them with far greater capabilities to engineer organisms than previous techniques allowed. The field of synthetic biology includes the relatively new ability to rapidly and inexpensively synthesize long pieces of DNA from chemicals, combined with improved methods for genetic manipulation and design of genetic pathways to achieve more precise control of biological systems. These advances will help usher in a new generation of vaccines and other innovative medical treatments, and equally important, improved understanding of basic biology that will help us to continue solve biomedical problems.

Synthetic biology is changing the nature of *basic molecular biological research* and our understanding of basic biology. As DNA synthesis becomes ever less expensive, researchers will be able to use synthetic biology to rapidly change the DNA sequence of various genes or whole genomes, allowing them to understand basic cellular functions in a rigorous way. Prior to synthetic biology, investigators could only manipulate one or at most a few genes in any given experiment, resulting in a relatively slow discovery process. My laboratories, along with others globally, are using the tools and approaches of synthetic biology to understand the mechanisms of evolution at the molecular level, to define regulators of specific genes or gene pathways and to establish, at the molecular level, the minimal requirements for life.

On this latter topic, for over 15 years researchers at JCVI have been working to construct a “minimal cell”, a living cell with the minimal set of genes that can still sustain cellular life. In 2010, we announced a seminal milestone: the creation of a bacterial cell controlled by a chemically synthesized genome. Several of the basic tools of synthetic biology were developed as part of this long-term project. It is our hope and belief that the chemically synthesized minimal genome, once complete, will be used by scientists worldwide as an experimental platform to understand how cells function. Such basic understanding of the rules of biology is vital for continued biomedical progress.

As I mentioned I also head two for profit biotechnology companies. Let me outline a few of the important programs underway there in which we are applying the basic science research of synthetic biology.

In 2013, a team of international researchers from JCVI, SGI, Novartis Vaccines and Diagnostics, and the Biomedical Advanced Research and Development Authority (BARDA, US Department of Health and Human Services) developed new methods to rapidly generate influenza vaccine seeds by using synthetic biology tools and technologies. This method will enable a more rapid pandemic response and yield a more reliable supply of better matched seasonal and pandemic vaccines than are currently available.

That same year, CDC and BARDA requested that the team use this method to develop a vaccine against a new strain of bird flu (H7N9) that appeared in China. BARDA is currently stockpiling that vaccine.

SGI scientists, in collaboration with Lung Biotechnology, Inc., a subsidiary of a local biotechnology company, United Therapeutics, are applying synthetic biology techniques to solve a very different problem: the chronic shortage of lung transplants available to the 400,000 people who die annually from various forms of lung disease. The hope is to develop methods to overcome the genomic incompatibilities that prevent animal lungs from being used in people. Employing the new tools of synthetic biology—DNA design, DNA synthesis, genome editing, and genome modification tools—our two companies hope to create animal organs that are safe and effective for use in humans.

SGI is also developing new nutritional products using algae. The company has partnered programs to develop omega 3 supplements such as DHA, EPA and astaxanthin through genetic engineering and strain selection of algae. SGI continues to explore the possibility of using algae to develop cost effective algae-based biofuels.

I along with all my teams consider the ethical and societal implications of the work to be as important as the scientific research. We examined ethical concerns before beginning any actual experiments or research into constructing a minimal cell or the work to construct the first synthetic cell.

In 1999, we convened the first ethical review of synthetic biology by a panel of experts at the University of Pennsylvania. The panel's independent deliberations, published in the journal *Science* along with the scientific minimal genome research, concluded that there were no strong ethical reasons that should prevent the team from continuing research in this field as long as they continued to engage in public discussions, which we have continued to do so today.

In 2007, JCVI, along with researchers at MIT and the Center for Strategic and International Studies in Washington, DC, completed a two-year study of biosecurity and biosafety concerns associated with synthetic biology and presented and evaluated a series of policy options for consideration by policymakers. One of those options was issued as guidance by HHS in 2010 for firms that sell synthetic DNA. All major providers, including SGI DNA, follow this screening guidance.

JCVI recently completed a study funded by the Department of Energy, examining how well the current U.S. regulatory system for genetically engineered products will be able to handle anticipated products engineered using synthetic biology. Our conclusion is that U.S. regulatory agencies (FDA, USDA, and EPA) have adequate legal authority to address most, but not all, potential environmental, health, and safety concerns posed by the new technology.

Finally, I should add that ethical issues related to synthetic biology were reviewed by the Presidential Commission for the Study of Bioethical Issues. The 2010 study, “New Directions: The Ethics of Synthetic Biology and Emerging Technologies”, recommended that the government “remain forward-looking about the potential benefits and risks to the public”, but did “not recommend that additional agencies or oversight bodies need to be created to oversee synthetic biology.”

What are your views on how federal science agencies should approach funding on important biomedical science research? What specific recommendations do you have?

The United States is fortunate to have a robust federally funded science program in the form of the National Institutes of Health and the various federal agencies such as the Centers for Disease Control. While there are classic examples of how our government has been key to moving new fields forward such as space exploration and NASA, my experience is centered on the NIH and the human genome project. I was a researcher with NIH in the late 1980s and early 1990s and was privileged to be involved in some of the earliest discussions about a large scale project to tackle sequencing of the human genome.

Fourteen years ago on June 26, 2000, President Clinton, Francis Collins of the NIH, and I, representing Celera Genomics, announced the first sequence of the human genome. My team at Celera spent \$100 million over 9 months to obtain our sequence using a then novel approach called whole genome shotgun sequencing, which is now an industry standard. It’s just recently become possible to sequence a human genome for around \$1,500 in just a few days. This represents a phenomenal rate of cost and capability improvement even exceeding improvement in computer chips known as Moore’s Law.

Recent progress with the use of genomics to improve the treatment of some cancers is likely just the beginning of a genomics-based revolution in human health and the practice of medicine. The ALK gene is a good example. ALK, or “anaplastic lymphoma receptor tyrosine kinase”, is responsible for signal transduction and can be switched on or off. Altered forms of this gene, those that do not regulate normally and are permanently switched on, are present in a variety of cancers and occur in about 4% of non-small cell lung cancers. Pfizer developed a drug called Crizotinib (aka Xalkori) that was FDA licensed in 2011 that blocks the carcinogenic kinase activity of the ALK gene and significantly increases progression-free survival of non-small cell lung cancer patients with the ALK mutation. This is just one example of how utilizing information from the human genome can aid in development of better and more targeted therapies, can identify patients that will likely benefit most from certain therapies, and ultimately, lead to improved clinical outcomes.

The advances in genome sequencing and availability of large-scale cloud-based computing platforms are opening an important new opportunity in biomedical science research but substantial challenges remain. To date most human genomics research has focused on: 1) a small part of the genome mostly on exons, the parts coding for proteins and often looking only at single nucleotide polymorphisms or SNPs even though we know that the whole genome is vitally important to human health; 2) haploid or non-diploid genomes which do not give researchers the complete parental lineage of the individual thereby being unable to resolve compound heterozygote alleles that are likely quite important in human health; 3) variations found in germline and somatic human cells, ignoring the human microbiome, the trillions of bacteria living in and on our bodies with diverse genomic and metabolic functions and are inextricably linked to human health and; 4) small study populations unable to identify rare genetics events occurring on the level of 1 in 50,000 people that again are likely to be critically important in human health.

Federal science agencies could dramatically accelerate progress in genomics by recommending a new set of guidelines for funding federal research involving human subjects. Such guidance should include a presumption that human clinical trials require whole human genome sequencing by a qualified laboratory using the latest technologies and bioinformatics methods. These recommendations should include a requirement for full characterization genomic and functional characterization of the human microbiome. Such a requirement would spur private and public sector efforts to address the next frontier of challenges in genomics at relatively low cost to the government.

Setting this guideline will require bold leadership because of the multitude of sensitive and critically important national and international ethical, social, and legal issues. The time to act is now. I expect that pharmaceutical companies will rapidly adopt a whole human genome sequencing standard because their economic incentives are highly aligned with the use of these

data to identify new drug targets, and the potential to increase the therapeutic efficacy of candidate drugs through targeted genomics-based enrollment.

A federal standard requiring whole human genome sequencing for appropriate government-funded human trials should be accompanied by a federal research commitment to also accelerate progress in identifying opportunities to improve human phenotype technologies and methods used in medicine. Phenotype is the general term used to describe the physical, biochemical, and physiologic characterization of humans and other living things; this information is essential to understanding genomics. Despite the progress made in electronic medical record adoption, the medical enterprise remains a largely narrative enterprise. As an example, the current standard for reporting the results of magnetic resonance imaging or MRI is a one- to two-paragraph description of the radiologist's interpretation in the form of a report back to the ordering physician. This is generally inadequate for the quantitative analytics needed to find genomic associations.

At Human Longevity, we've partnered with CorTechs Labs, a company formed to commercialize technologies and research done at the University of California San Diego that has an FDA approved method and software to translate MRI into quantitative neuroanatomical volumetric data. For example, using the NeuroQuant product from CorTechs Labs we can capture the exact volume of the hippocampus, a part of the brain that's important for memory and shows remarkable changes in Alzheimer's disease. We need similar technologies and methods yielding high quality quantitative data across all domains of the human phenotype. This extends even beyond the current medical domain and includes the need for much better characterization of family history, environmental exposures, and social and behavioral determinants of health. The availability of and interest in mobile smartphones and other new sensors to passively characterize human various activities related to health may provide valuable new data in some of these domains.

I think setting a new standard requiring whole human genome sequencing for appropriate government-funded human trials would also accelerate critically important progress in genomic-related regulatory policy in the US and globally, spur an increased commitment by medical schools and allied health professional schools to training in medical genomics, and provide a basis for renewed efforts in public dialogue about the role of genomics in human health and the practice of medicine.

How important are non-government research efforts in advancing drug discovery and developing innovative treatments? How do these efforts complement or compete against government investment on these problems? Are government policy incentives properly structured to encourage private sector investment to make medical breakthroughs?

Government-funded research alone is clearly insufficient to solve the biomedical challenges facing society today. This is now especially true given the recent decline in NIH funding. Research at not-for-profit independent research institutes such as JCVI and at universities across the country is suffering.

The private sector must not only do their share, but also pick up the slack. This is one reason I recently launched my new company, HLI. HLI has raised \$80 million dollars to build the largest human sequencing operation in the world. We plan to build the most comprehensive and complete human genome, microbiome, and phenotype database available to tackle the diseases associated with aging-related human biological decline.

HLI's goal is to change the way medicine is practiced by helping to shift to a more preventive, genomic-based medicine model, which we believe will lower healthcare costs. The goal is not necessarily lengthening life, but extending a healthier, high performing, more productive life span.

In brief we are attempting to build the world's most advanced proprietary human health data base including whole human genome sequences, microbiome data, proteomics, and metabolomics along with extensive human phenotype data. We are going to try to overcome the major challenges I highlighted earlier including: using the whole sequence instead of just part of the sequence, trying to get to diploid genomes to resolve compound heterozygosity, correlating the human genome with the microbiome, and finally, and maybe most importantly, doing this at a much different scale than has ever been attempted.

We plan to complete our first 1000 human genomes next month. By the end of calendar year we will be at an installed capacity of 40,000 genomes per year and plan to increase capacity steadily. We plan to sequence 50,000 genomes in 2015, and to have the capability to run 100,000 human genomes per year by the end of 2015. By 2020, we anticipate we will have more than one million human genomes in our database. Our bet, and the risk our investors are taking with us, is that if we can do this, solving the numerous genomic, bioinformatics, and phenotype challenges, we may reveal many new clinically actionable associations and by doing this we hope to revolutionize the practice of medicine. I think that at some point in the near future everyone will have their whole genome sequenced, and this sequence will be an essential foundation for our health and the practice of medicine. I may be wrong though. We are going to try the experiment to find out.

HLI's and similar privately funded research complements and builds upon government investments in these areas. Both research funding streams must remain strong if we are to make rapid progress applying genomics and synthetic biology to produce medical breakthroughs. One

of the best ways to encourage private sector investment is to continue to fund research in the basic biology that underpins future biomedical advances.

Government and non-government research efforts are essential for progress in biomedical research science. The Human Genome Project and my efforts with Celera Genomics provide a good example. The scientific leaders who requested \$3B of funding from Congress in 1989 to pursue the Human Genome Project and the Executive and Legislative leaders who that approved of this project represent America at its best. The progress made in government and non-government genomics research would not have occurred without this leadership. My decision to leave the my not for profit research institute in 1998 and pursue an independent private sector effort for human genome sequencing using a “whole genome shotgun sequencing” approach is a good example of the value of the private sector accepting a risk the government-sponsored Human Genome Project would not. Taking this risk led to innovation that today is standard and responsible for much of the progress that’s been made in genomic sequencing. However, there are many examples where taking this risk does not pay off and companies fail, but this why it’s such an important complement to governmental research efforts. Government research should establish useful directions and create platforms for the private sector to build on and use to take risk and fail or succeed, whether it’s computation and the digital computer, the space program, the Internet, the Human Genome Project, or the Brain Initiative.

I’ve advocated for you to consider establishing a new federal standard requiring whole human genome sequencing for appropriate government-funded human trials. My company HLI would benefit from establishing such a standard, but so would many other for-profit, non-profit, and governmental research organizations. We all benefit from the competition this would generate and all of our families and communities will win through better health and better medical care at affordable costs. I appreciate the opportunity to share some of my thoughts with you today, and I look forward to further discussion and progress.

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J. CRAIG VENTER, Ph.D., is a biologist renowned for his contributions in sequencing the first draft human genome in 2001, the first complete diploid human genome in 2007 and construction of the first synthetic bacterial cell in 2010. He is founder, chairman and CEO of the J. Craig Venter Institute (JCVI). He is also a co-founder and CEO of Synthetic Genomics Inc (SGI), a privately held company focused on developing products and solutions using synthetic genomic technologies; and a co-founder and CEO of Human Longevity Inc (HLI), a privately held genomics and cell therapy-based diagnostic and therapeutic company focused on extending the healthy, high performance human life span. He and his teams are focused on a variety of projects and programs including: synthetic genomic research and the application of these advances to develop new vaccines and food and nutritional products, new biofuels and biochemicals; continued analysis of the human genome including the human microbiome, and discovering and understanding genetic diversity in the world's oceans. Dr. Venter is a recipient of the 2008 National Medal of Science and is a member of the National Academy of Sciences. He is the author of *Life at the Speed of Light: From the Double Helix to the Dawn of Digital Life* (Viking, 2013) and *A Life Decoded: My Genome: My Life* (Viking, 2007).

Chairman BUCSHON. Thank you, and I agree. This is an exciting time in health care. I miss health care. I have been out of it now for four years. From an overall federal budget standpoint, usually when I am at a hearing, and we are talking about discretionary funding programs, I like to say that right now in Washington, D.C., unfortunately, we are not addressing the entire piece of the federal spending pie. And—I will. I recognize myself. Because he pointed—he told me I had to, so I do, for whatever time I have left.

And that is a challenge, because many people know that 60 or 65 percent of all federal spending right now is mandatory spending, and the remaining part is discretionary spending, including Department of Defense, and that is where we start to see discretionary programs, like research funding, being pinched in an effort to balance the overall federal budget.

So I am hopeful that in the next number of years, or short time-frame, that we will begin to address the entire piece of the pie, and take some of the pressure off the discretionary spending, particularly research funding, which I think many—most of us on this panel would agree needs—is extremely important, and needs to be probably increased to keep up.

I will ask Dr. Venter this question. The return on investment on R&D, like in the pharmaceutical industry, has been a subject of recent debate because there are companies that are adept at R&D, and these returns can be significant both—from a both clinical and economic perspective. However, out there there are some forces that are, specifically in the health care industry, that have maybe the opposite perspective, people that are controlling companies, and believe that R&D is no longer productive in the private sector, for example. And you—seeing this, as some companies are bought and sold, that some people don't value the R&D that was being done by the company.

Do you disagree with this? Can we talk about the benefits of robust R&D, at the same time the potential consequences of cuts to R&D budget in the private sector, based on the shareholder investment in the companies?

Dr. VENTER. Well, I think the experience that I have, and if you look at the biotech industry as a whole, it is largely based on basic research. It is only when you get way past that, into the manufacture and development of drugs, that I think you get into some of those conflicts.

What I see is many people turn to biotechnology, and the robust funding that we have with capital investment, as an alternative way to fund basic research, because every breakthrough that we rely upon in the field of synthetic genomics, we have been doing basic research there for eight years. With these new efforts to sequence large numbers of human genomes, and have them impact medicine, these are large research projects that, in their places, are taken on by government funding, not by private capital.

So I see it from the opposite point of view. I see much more private money, private investment, going into supporting basic research, because it is—I think we all agree, it is the basic research that drives these breakthroughs in every field.

Chairman BUCSHON. Yeah, I would agree. R&D research in the private sector, you know, is important, and hopefully we can con-

tinue to encourage all of our companies to continue to value this as a very valuable thing.

Dr. Varmus, in your opinion, do we have the right balance between basic and applied science research, particularly in the biomedical science? Do we spend too many resources, or over-emphasize applied science—sciences at the expense of basic science research? Do we—where is that balance? Where do you see that?

Dr. VARMUS. Well, thank you for the question, Chairman. It is—

Chairman BUCSHON. Turn on your mike.

Dr. VARMUS. —quite difficult—sorry. This is a very difficult thing to measure, because the definitions of basic versus applied science, especially in this day and age in which the approach of basic science to clinical application is very, very close. I would argue, based on my observations, it is hard to document numerically that there is, in this moment of difficulty in obtaining funds for research, a tendency to think more about how the research that is being done, even in government supported labs, can be applied to the very real problems of human disease, and that this creates a situation in which scientists think their chances of being funded are augmented, and it may well be, by making specific claims for how the work they do will be applied in the short run.

We have tried to defuse that somewhat recently at the National Cancer Institute by announcing a new award, a seven-year outstanding investigator award, that provides stable funding for at least 50 percent of an investigator's work, so they are more willing to take risky approaches to science, to say, this is an important question. I don't know where it is going to come out, it may or may not be useful. That is an element that we need to protect, and I—and we are making an effort to do that.

I would say one more thing about the previous question you asked, about research in companies, and I agree with Craig that the major companies do recognize the importance of research. In my observation over the last few years, large companies and small are more willing to come to the NIH to work with us, we doing more of the more basic work, they bringing in the more applied approach.

And we see this in the design of our clinical trials, where—which are increasingly becoming dependent on genetic analysis of tumors, targeted therapies being provided for tests by the companies, companies eager to collaborate with us, either through the NIH Foundation, or through work that we do at the NCI.

Chairman BUCSHON. Thank you very much. I now recognize Mr. Lipinski for his questions.

Mr. LIPINSKI. Thank you, Mr. Chairman. I want to start with Dr. Keasling. And I just want to say, Dr. Keasling, it was—trying to remember how many years ago, five or six years ago, that I came out to JBEI specifically at that time mostly to look at the bioenergy work that was going on there. But I wanted to ask you about technology transfer.

You successfully co-founded a company, Amyris, to bring your discovery to the marketplace, so I would like you to talk about the challenges that you have faced trying to launch your company, or otherwise transfer your discoveries into commercial applications,

and then talk about what role do you see federal government can play at helping transfer academic research into the marketplace, and touch on what—at what stages should the federal government be involved, and what is the best way for the federal government to be involved?

Dr. KEASLING. All right. So I will start answering that kind of—the last part first, and that is that the work that went into the anti-malarial drug was based on basic science that we did that was funded through the National Science Foundation to try to understand how microbes produce cholesterol-like molecules, and how plants produce molecules that are flavors and fragrances. And we then took that science, and engineered a microbe, and happened to learn about this anti-malarial drug.

And that attracted funding from the Bill and Melinda Gates Foundation that allowed us to both develop this microbe, but also build Amyris, a company that makes no profit, and neither does Sinofi-Aventis, on this anti-malarial drug. In fact, they gave the technology away. It is being used free. And so did the University of California, which has title to the patents.

What Amyris was able to do was take that same microbe that produces the anti-malarial drug and swap out a few genes, put in a few others, and it produces a diesel fuel that is now running in buses in Sao Paulo and Rio. In fact, they have clocked about five million miles on that diesel, and is now a molecule that is in flavors, and fragrances, and cosmetics. In fact, you can buy cosmetics from these yeast produced molecules.

Our ability to get that technology out to companies is critical. Amyris came into the University of California, licensed that technology, and that allowed them to build the company. And that—federally funded research, and research funded by the Bill and Melinda Gates Foundation made all of that possible.

I think it is critical that the federal government continue to fund basic science and basic research because, as we heard in this hearing today, that leads to the development of companies, and those companies tend to be located near the science that is being done so they can have access to those scientists, and build the companies further. Amyris now has about 400 employees, about 500, actually, in the U.S., and in Brazil, that are working on producing more molecules like this that will make the U.S. competitive.

Mr. LIPINSKI. Thank you. And you had talked about doing a—the time may be right for some kind of national initiative. What would—you think that would—should look like?

Dr. KEASLING. I think that the U.S. could, and should, make investments in biomanufacturing. And generally, in this area of engineering biology, we have been the leader since the discoveries of genetic engineering in the early '70s. But that leadership is being challenged by China and many other countries, and they are building on a lot of the discoveries here, and the fact that we don't have federally coordinated effort. An effort that would coordinate all the federal agencies, so that they are moving in the same direction toward engineering biology, I think, could have a huge impact on the field, and also on our national economy.

As I mentioned earlier in my talk, this area is an area that is growing rapidly, and will continue to grow. We want to make sure

that it grows in the United States, and an effort by the federal government around engineering biology could ensure that.

Mr. LIPINSKI. Do any of the other witnesses have any comments or suggestions along those lines?

Dr. TESSIER-LAVIGNE. I just want to reinforce the last point, that the basic science discoveries and their commercialization leads to—not just to great outcomes, like the generation of these molecules or new medicines, it also creates real economic activity locally, as the industry will locate next to the sites of innovation.

Mr. LIPINSKI. Thank you. And Dr. Varmus or Dr. Venter, any—

Dr. VARMUS. Well, I just would emphasize that, at the Cancer Institute, for example, the fundamental tools of genetic engineering are in use almost every day to change the behavior of cells, experimental animals that allow us to probe the secrets of cancer more profoundly, and new developments in this area are much to be welcomed by us in our experimental approaches to cancer.

Mr. LIPINSKI. Thank you. I yield back.

Chairman BUCSHON. Thank you. Recognize Mr. Johnson from Ohio, five minutes.

Mr. JOHNSON. Thank you, Mr. Chairman, and really appreciate our witnesses being here today for this hearing. I am an information technology professional for most of my life before I came here to Congress, so I am always looking at how advances in technology affect different industries, particularly yours, so I would like to go in that direction just a little bit, if I could.

So, for Dr. Varmus and Dr. Venter, if you would, you know, we are increasingly seeing the need for big data to help us decipher scientific problems, including understanding the genome, and complex diseases, like cancer. What is the future of cloud computing and big data in biomedical science research, and what role will they play, do you think?

Dr. VARMUS. Thank you. This is a very timely question, because the NIH, and NCI in particular, are now housing the largest data sets in the world as a result of the accumulation of genetic information about cancer. As you may understand, cancer—

Mr. JOHNSON. But can't find Lois Lerner's e-mails, go figure.

Dr. VARMUS. No comment.

Mr. JOHNSON. Go ahead, go ahead.

Dr. VARMUS. As you know, cancer is a disease largely driven by changes that occur during life and genomes, and being able to understand the patterns which differ from every tumor to another is critical. We had built, through the exercise I mentioned, The Cancer Genome Atlas, a huge database that needs interpretation.

The question about cloud computing is particularly apt for us at the moment. We now have a—we are about to launch a cloud pilot exercise in which we will fund three—two or three competitors to do experiments with cloud computing, to allow investigators around the world to work with our lab's large data sets. The NIH more generally has an initiative called Big Data to Knowledge, BD2K, that was attempting to learn both the computational rules that will make best use of that data, but also to do so in the context of privacy, which is important in medical research, and in a way that al-

lows fair access of our investigators throughout the world to those data sets.

In addition, there is a movement underway internationally to create something called a Global Alliance for Genomics and Health that will—has attracted the attention of literally hundreds of institutions around the world to be sure that data sets, initially in the area of oncology, and various genetic diseases to have access to those data sets, both to understand the underlying nature of the disease, and to make informed decisions about prognosis and treatment of those diseases.

Mr. JOHNSON. Okay. Thank you. Dr. Venter?

Dr. VENTER. Thank you for your question. It is—it is, as Harold said, very timely. There are two thresholds we just passed that actually allowed us to form Human Longevity. One was a sequencing technology that just barely passed the threshold of cost and accuracy.

But the most important changes are in the computer world, and we are going to rely very heavily on cloud computing, not only to house this massive database, but to be able to use it internationally. We will have operations in different parts of the U.S., and even in Singapore, to allow us to do computation 24 hours a day. The cloud sort of makes that seamless, instead of trying to transport this massive amount of data.

Trying to move things from my institute in Rockville, Maryland to La Jolla, we had dedicated fiber, but it is now so slow with these massive data sets, we use Sneakernet or FedEx to send discs, because we can't send it by what you think would be normal transmission. So the use of the cloud is the entire future of this field.

Mr. JOHNSON. Okay. All right. Well, Dr. Varmus, in your written testimony you discussed how supercomputers have created a powerful tool to analyze massive, complex data sets for genomics, proteins, and other biological sciences. In my final 30 seconds here, do you think that if the Department of Energy and National Science Foundation developed the next generation of computing—supercomputing, moving from petascale to exascale level, that even more medical breakthroughs would be made possible, and is supercomputing capabilities a limiting factor for future medical breakthroughs?

Dr. VARMUS. Yes, absolutely, and we—this, in some way, would—we would obviously capitalize on that for its—the DOE's agencies. We have, in the past, used DOE beam lines for our structural biology work. As Craig mentioned earlier, the number of genomes being sequenced is accelerating very rapidly, and the ability to sift through all that information, to look for patterns, to look for common mutations, and different tumor types, to try to understand the biological events as revealed by genetic analysis to the clinical events of real life experiences that the patients had is going to be a tremendous task that is going to—we have not yet achieved in solving simply by sequencing these genomes. We need to understand what those patterns mean, and it is going to require a tremendously heavy lift in the computer world to do that.

Mr. JOHNSON. Okay. Well, thank you very much. Mr. Chairman, thanks for giving me the additional time.

Chairman BUCSHON. You are welcome. They are—we are going to have votes probably in the next five minutes or so, but once they call the vote, we still have plenty of time. We will be able to finish our line of questioning, and—so I now recognize Mr. Peters.

Mr. PETERS. Thank you, Mr. Chairman. I want to thank all of you for being here, particularly my constituent, Dr. Venter. And we are so proud, and awed, and excited by what you have accomplished in the genome.

And what I was—what—as I was listening to the testimony, and looking over some of what you presented, it strikes me that you, in particular, are someone who has been on both the private and the public side of this. And we have been talking for the last year, the model that we followed here with the NIH is that we provide a lot of funding, and much of it is competed, so that you have scientists who file these applications for grants. It is very competitive, it is peer reviewed, and that has been the basis of a lot of our science.

And what I am inferring from this discussion is that now there is more a private sector kind of involvement, a lot of the—it is not the same model. So how should I, as a policymaker, be thinking about this, and is the old model, the model that has kind of been our playbook and so successful, is that still the same, or is that changed?

Dr. VENTER. Well, thank you for the question. It is a very important one to answer—I also spent ten years in government at the NIH—

Mr. PETERS. Right.

Dr. VENTER. —so I think I have been institutionalized many times. So I think the challenge, and the risk I see with government funding, aside from, as Harold said, the decreased buying power of it is the increased risk aversion of that funding. And I am pleased to hear what he says about the seven year grants. I think that is a step in the right direction.

Finding a way to set aside a certain percentage of NIH funding to mandate risk is a challenge, and I can tell a story about it. With a previous NIH director, they started this new award for high risk research, and I was on the committee with other successful researchers, and the top 10 people we listed for this award were rejected because they were too risky.

Mr. PETERS. Too risky, right, yeah.

Dr. VENTER. So the challenge is how do you legislate risk taking when it is sort of not built into the fabric of the people and the government? But somehow we have to take greater risk with this funding to get more value for that funding.

Mr. PETERS. Did that used to happen on the natural because there was more funding? And one of the things I have heard is that, because of the reduced buying power, the reduced investment, effectively, only the safe stuff is getting done, that if there were more funding, it is alleged that risky stuff would happen as part of the mix.

Dr. VENTER. Well, there was more funding per capita. There were almost an order of magnitude less scientists when I started in my—

Mr. PETERS. Right.

Dr. VENTER. —career. And the funding from the Cancer Institute, there was much more on reputation of the investigator versus the sort of negotiated contract of the next stage of the research. And it sort of had to go that way, I think, because of fewer dollars per the number of researchers. So, you know, there is no—I don't have a magic solution for it, but—

Dr. VARMUS. No. I—

Dr. VENTER. —we need to change something.

Dr. VARMUS. I don't have a magic solution. I would like to comment briefly on the question, which, of course, is a very important one. I don't think the model is essentially changed. I think—and it is important to remember that, while much of our research is conducted through grants that are given to competing extramural investigators, we also have other ways of doing research. For example, through an intramural program, where there is a lot more stability, and a chance to encourage risk taking.

And we also, within the NCI, have the privilege of having a contract laboratory, the national—the Frederick National Lab for Cancer Research out in Frederick, Maryland, where we can undertake projects that are extremely risky, like the new RAS initiative that I mentioned briefly in my testimony.

The question of how we get both investigators and reviewers to take risks is a tricky one, because everyone recognizes this is a limited pot of money, and when you have a good proposal that seems very likely to yield tangible results, everybody's focus tends to be on funding those first. And we have had to create programs, like our Outstanding Investigator Award, like the so-called Pioneer, and other innovation awards that are now awarded—

Mr. PETERS. Right.

Dr. VARMUS. —throughout the NIH to try to encourage risk. But it is not the NIH, it is the whole community that is seized with this anxiety about how to undertake funding that is most productive.

Dr. TESSIER-LAVIGNE. If I may just comment briefly also on the question.

Mr. PETERS. We together have 15 seconds. Yeah, go ahead.

Dr. TESSIER-LAVIGNE. The private sector is increasingly trying to tap into the discoveries in the basic science community, but they are not generating the knowledge, nor will they. So there isn't a change in that sense. There is still—nothing can substitute for the federal support of basic research.

Mr. PETERS. Well, thank you. Mr. Chairman, I appreciate the hearing. I yield back.

Chairman BUCSHON. And, again, we—they have called votes, but for the first vote, we probably have 20, 25 minutes to get there to vote, so we are going to continue on with our—with recognizing Mr. Hultgren for five minutes.

Mr. HULTGREN. Thank you, Chairman. Thank you all for being here. This is a very important hearing. It has been one of my primary goals on the Committee, to make sure that our laboratory system is set up, really, to provide the best bang for the buck, and to better work in our national interest. I just want to thank you for your work, and for your testimony here today.

With the great innovation ecosystem in Illinois, I have seen how labs provide a valuable resource to industry to do work in facilities

that no individual company could build. The federal government does have a role in this space. Use of facilities such as the advanced photon source at Argonne have provided companies such as Abbvie with the unique research capability to make groundbreaking discoveries.

What would normally take the company weeks on their own can be done in days with samples spending more in overnight deliveries than on the lab bench. My scientists at FERMI have also done key research in the accelerator technology necessary to finish the Linac Coherent Light Source upgrade at SLAC.

Yesterday I introduced a bill to help modernize the national labs with my good friend Mr. Kilmer from Washington, along with Chairman Smith, and other Members from the Committee. We are looking to make sure that these facilities are open to partner with industry when it makes sense, ensuring that discoveries are not stuck in the lab.

Dr. Tessier-Lavigne, how are the goals of pharmaceutical R&D different from federally funded research projects, and I wonder if you could explain—but also how can the federal government help to better accelerate innovation in this field?

Dr. TESSIER-LAVIGNE. Well, thank you. The goals in this sense are complementary, they are not different, but it is really a staged process, where the fundamental insights into what goes wrong in disease, whether it is asthma, or Alzheimer's Disease, or various cancers, are generated, for the most part, in the academic sector.

The companies really come in when the discoveries are breaking, when insights are starting to coalesce, and they sift through them to try to find the most promising ones, and then deploy their horsepower, which is really focused around taking those insights, taking molecular targets, which they believe will be good targets against which to make drugs, and then start to make the drugs. That long odyssey of drug making takes, on average, 13 years, and over a billion dollars. They do that part of the work.

The—so the research is complementary. It is not identical. There is some basic research, some fundamental research being done in the private sector, but very little compared to the academic sector, and vice versa. Some academic institutions will actually make drugs, and take them through clinical trials. Those are the exceptions that prove the rule.

And then at the interface, the small startup companies are very important in helping sift through the discoveries made in academia, and move them towards the private sector, with the big companies then partnering with them as well, and disease foundations providing an assist. So it is really an ecosystem with those four components.

How can we facilitate it? There is a lot of effort being placed right now on that interface. It is really about the interface. How can we ensure that discoveries in academia don't lie fallow, that people recognize them and develop them? And there are a number of initiatives that are being made on those fronts.

I mentioned in my testimony the Accelerating Medicines Partnership, which brings together the NIH, the Foundation for NIH, and 10 companies to focus on very important areas, like Type II diabetes and Alzheimer's disease, to try to identify the best molecular

targets. What are the best insights from academia? What are the biomarkers of the disease? What are the best targets for the biopharmaceutical industry on which to deploy its horsepower?

So I think it is initiatives at that interface that I think will yield the biggest bang for the buck. What we are not going to see is a change where the pharmaceutical industry does a lot of the basic research, or academia makes a lot of the drugs. But what we can really help with is that interface.

Mr. HULTGREN. Thank you. Dr. Venter, and also Dr. Keasling, what—are you concerned about any government regulations that might adversely affect both research and technology transfer of advances in synthetic biology?

Dr. VENTER. Thank you for the question. I have not seen anything at all. I think, you know, that the whole case of intellectual property being important in this new field I think is overplayed. I think, in this new field of applying genomics to medicine, and the rapid change of events in synthetic biology, it is first mover effects, and making great advances I would say are an order of magnitude better than IP is now. It is like the software industry. The changes are happening so fast that you can't really protect things with intellectual property as much as you can by just trying to stay ahead of the curve. My colleagues may disagree.

Mr. HULTGREN. Dr. Keasling, yeah, I wonder if you have any thoughts on government relations—or, I am sorry, government regulations that might adversely affect research and technology.

Dr. KEASLING. I don't think there is right now. We have had a very effective system that started with the dawn of genetic engineering. That system has changed over the years as the technology has changed, but it has proven very effective, and I think we should continue that regulation that works so well.

Dr. TESSIER-LAVIGNE. And if I may just—

Mr. HULTGREN. Quickly, I am out of time.

Dr. TESSIER-LAVIGNE. —that is right, comment on Dr. Venter's point, I think that his point really applies to tools and technologies, which evolve quickly. I think when it comes to the pharmaceuticals, there the patent system and IP protection is absolutely essential. Otherwise, the industry just won't invest.

Mr. HULTGREN. Thank you. I am out of time, and I know we have got votes, so I will yield back. Chairman, thank you so much.

Chairman BUCSHON. You are welcome. I ask unanimous consent to allow Mr. Rohrabacher to participate in the questions. Without objection, the Chair recognizes Mr. Rohrabacher for five minutes.

Mr. ROHRABACHER. Thank you very much, Mr. Chairman, and let me note, on the last point that was just made, that patent rights have been considered vitally important to American progress from day one. In fact, it is the only right that is written into the body of the Constitution as the word right. The Bill of Rights came later. And the fact that we have had a diminishing of patent protection in our country is of great concern to me, as is the fact that we have had a medical device tax as a vehicle to try to provide some kind of mechanism. Seems to me to be showing that perhaps there isn't as much appreciation for technological advance in the higher circles that we should have.

Also let me just note that the FDA has recently approved Al Mann's ten year question to have an inhaler being used as a substitute for needles for diabetics, and in the treatment of diabetes. And it took him ten years and a billion dollars. These are things of great concern. That can't go on. Having something held off the market for that long, and that expensive—added to the process are reasons for concern.

But today, Mr. Chairman, I would like to ask the panel about another flaw in the system. I would like to submit with a—for the record an article from the New York Times.

Chairman BUCSHON. Without objection.

[The information appears in Appendix II]

Mr. ROHRABACHER. This article details a real challenge that has surfaced in California, with a particular company that is being taken over by a hostile takeover. And it appears to me, after looking at this, and looking at the details behind this, that we have a basic flaw in our tax system, and in our basic corporate structure that we have set up that will discourage R&D in the private sector by companies.

And what we have here is Allergan, a company that has hundreds, if not thousands, of employees engaged in research is being taken over—a hostile takeover by a company who is actually raising the money for the hostile takeover by a plan that includes eliminating all the R&D. And thus you have a profit in eliminating R&D from a company by other companies wanting to take over.

I mean, this—if this methodology is seen by others, we are going to have basically a huge reduction—we have made it profitable for companies, then, to come in and eliminate R&D. Have any of you gentlemen got any thoughts on that? Or is this just maybe a new—

Dr. VENTER. I will—

Mr. ROHRABACHER. —concept—

Dr. VENTER. Yes.

Mr. ROHRABACHER. —here?

Dr. VENTER. This is not the—

Mr. ROHRABACHER. I didn't—

Dr. VENTER. —a—it is not a new concept to the pharmaceutical industry.

Mr. ROHRABACHER. Okay.

Dr. VENTER. CEOs will come in, and think they can greatly improve the bottom line by getting rid of R&D, and—

Mr. ROHRABACHER. Right.

Dr. VENTER. —that is true for a very short period of time, but they basically bankrupt the company very quickly for doing that. So anybody who takes that philosophy is just—

Mr. ROHRABACHER. Well, this—

Dr. VENTER. —extremely shortsighted.

Mr. ROHRABACHER. Well, then, this is really a—well—short-sighted. They are not shortsighted for themselves. That is the whole point. They give themselves a million dollar bonus and buy a new yacht because they have now given themselves a profit at the expense of perhaps things—discoveries that could be made that would improve the lives of all of us ten years down the line. This is a catastrophe. This is a catastrophe for people whose lives will

now not be helped by the R&D that Allergan, and other companies like it, are conducting. And we need to correct this flaw in the system.

All these other things I have heard today are important, but I am really—Mr. Chairman, I commend you for calling this hearing. And the fact is that—but what we are—what—this whole issue that I just brought up, this undercuts so much of whatever the government's basic research is doing, and all the other things that have been mentioned, if our own private companies that invest in it, now we found—we have made it profitable for other companies to take them over and eliminate it. We are going to—our people are going to suffer needlessly in the future because of this.

Mr. Chairman, again, thanks for holding this hearing. All of the points that were made today are really significant. I have learned a lot, and I appreciate your leadership in this issue.

Chairman BUCSHON. Thank you, Mr. Rohrabacher. At this point I would like to thank all the witnesses for your testimony. This is very valuable testimony, as our Subommittee, and the full Committee, look to reauthorize National Science Foundation, and are very important in funding, you know, research, obviously. And the Members, thank them for their questions.

The record will remain open for two weeks. There may be some additional written questions sent to you that didn't get covered today from the Members, and just please respond to them as timely as you can. We appreciate your testimony. The witnesses are excused. The hearing is adjourned. Thank you.

[Whereupon, at 10:18 a.m., the Subcommittee was adjourned.]

Appendix I

ANSWERS TO POST-HEARING QUESTIONS

ANSWERS TO POST-HEARING QUESTIONS

Responses by Dr. Harold Varmus

HOUSE COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
SUBCOMMITTEE ON RESEARCH AND TECHNOLOGY

“Policies to Spur Innovative Medical Breakthroughs from Laboratories to Patients”

Dr. Harold Varmus, Director, The National Cancer Institute

Questions submitted by Rep. Larry Bucshon, Chairman, Subcommittee on Research and Technology

1. The 2011 SBIR/STTR reauthorization bill supports a pilot program at the National Institutes of Health (NIH) for “proof of concept” research. Specifically, this program allows NIH to award competitive grants of up to \$1 million to universities and other research institutions, which then award grants to investigators for activities such as prototype development, market research, or developing an intellectual property strategy. In what specific ways is the NCI involved with this program? What grants have been awarded to date? Is the program achieving its intended goals, and how could the program be improved? Please explain.

In response to the 2011 SBIR/STTR reauthorization bill the NIH developed a new program, the Research Evaluation and Commercialization Hub (REACH) program. This pilot program supports the proof of concept phase of technology development, or phase 0. The REACH program is trans-NIH; therefore all Institutes and Centers are eligible to participate and it is open to a broad range of technologies. The NCI SBIR/STTR program will contribute about 16 percent of the \$3 million total costs expected for the REACH program.

The first Funding Opportunity Announcement (FOA) for the program was posted April 25th, 2014 and the application deadline was June 26th, 2014. We anticipate issuance of the first set of REACH awards in the spring of 2015. As these grants are yet to be issued, we are unable to evaluate whether REACH will achieve its intended goals or if it needs to be improved, but NCI will assess the impact of this program after grants are awarded and at least some research has been done.

2. What is the NCI policy for the number of publications listed in the biosketch portion of a researcher’s grant application? Why is this policy in place, and what motivated it?

The NIH will require use of a new form of biosketch for all grant applications beginning in Fiscal Year 2016, and is now conducting pilot experiments to fine tune the application instructions and guidance to reviewers. The current pilot allows up to five pages for the entire biosketch, with a description of up to five significant contributions to science, including accounts of the impact of the contributions on relevant scientific fields and accounts of the applicant’s role. Applicants are permitted to annotate each contribution with up to four publications, and they may include a link to a complete list of publications.

The NIH is adopting this change towards requiring a narrative-based exposition of achievements, based on the success of a similar approach used by the Howard Hughes Medical Institute and

several other research institutions. Using a narrative rather than a list of publications is expected to improve the evaluation process for both applicants and reviewers. By generating an account of their own work, an applicant can explain the significance of the scientific advances associated with his or her work. For those involved in team science, it allows the investigator to describe his or her specific role in the work. Using this new form of the biosketch will give reviewers the ability to evaluate an applicant based on actual research accomplishments, rather than by the number of publications, the journals in which they appeared, and the position of the applicant's name in the list of authors.

3. What are three promising areas of cancer research today, and why are you particularly excited about their prospects?

This is a time of remarkable opportunity in cancer research and there is no shortage of areas of research to pursue. Here are three that I see as particularly promising:

Cancer immunology is rapidly and dramatically altering our understanding of host defenses in response to cancers and generating new therapeutic approaches to cancer. After years of uncertainty about the potential of the immune system to defend against cancers, basic research on the immune system has produced several strategies for immunotherapy, including antibodies against tumor-specific cell surface proteins; toxic fusion antibodies against cancer-cell related proteins; use of tumor-infiltrating T cells; and the generation of genetically modified T cells that attack specific tumors.

Genetically-based ("precision") oncology is transforming the diagnosis and treatment of cancers. The recent cataloging of the molecular attributes of adult and pediatric cancers reveals that each cancer has features held in common with other cancers of the same tissue type, as well as unique attributes. These features are increasingly being used to classify tumors, make predictions about outcomes, choose therapeutic strategies, guide the development of new drugs, and stratify patient populations in clinical trials.

The important role of **cancer in global health** is now widely appreciated, with the expectation that cancer will cause about 13 million deaths per year by 2030, with much of the increase in developing countries, where 25% to 50% of cancers may be related to chronic infections with viruses, bacteria, or parasites. By developing global cancer registries, implementing prevention and screening methods for common cancers, using available vaccines for hepatitis B and papilloma viruses, and improving access to cost-effective treatments, there is enormous potential to save lives and prevent suffering around the world.

4. Several articles in respected publications have commented on the issue of research reproducibility? including (but not limited to):

- "Reducing Our Irreproducibility" (Nature Magazine, April 2013);
- "Trouble at the Lab" (The Economist, Oct 2013);
- "Addressing Scientific Fraud" (Science Magazine, Dec 2011);
- "Must Try Harder" (Nature Magazine, March 2012);
- "How Science Goes Wrong" (The Economist, Oct 2013);

- “Redefine Misconduct as Distorted Reporting” (Nature Magazine); and
- “Misconduct Widespread in Retracted Science Papers, Study Finds” (New York Times, Oct 2012).

It appears that the inability to reproduce scientific claims is becoming a serious problem. What are the causes behind this growing problem? What are your recommendations to prevent this problem from becoming more serious?

As you noted, multiple reports of failures to replicate data have appeared recently in scientific journals and the mainstream press, prompting great concern in the scientific community. In response, the NIH as a whole, and a few individual institutes, especially the NCI and the National Institute of Neurological Diseases and Stroke (NINDS), have taken leadership roles by holding workshops with various constituencies to analyze the problems, suggest solutions and by making plans to improve the situation.

The workshops and a trans-NIH committee, with input from these stakeholder conversations, identified many possible causes of failures to reproduce data. Poor experimental design and inadequate statistical power were high on the list. Pressure to produce important findings and to publish in prestigious journals in the current hyper-competitive atmosphere of biomedical research also is likely to contribute. While misconduct in science (falsification, fabrication or plagiarism) may produce non-reproducible results, flagrant misconduct is thought unlikely to be a major factor in the apparent increase in non-reproducibility.

The NIH has been advocating a number of measures to improve rigor and reproducibility of research findings. These include workshops, talks, and published essays that address the situation and increase awareness among scientists and journal editors¹; improved instruction in experimental design in scientific methods; and the use of checklists to assure that methods, such as statistical power analyses and sample size calculations, are documented in grant applications, clinical trial protocols, and papers for publication. Efforts to reduce the underlying hyper-competitive atmosphere and to improve the opportunities for publishing negative findings are also under consideration. The NIH Office of Intramural Research will pilot a new module on research integrity as it relates to experimental biases and study design, and will add this to its required training for intramural researchers, and make it available to the extramural community. Other pilot projects will evaluate the scientific premise of grant applications, develop checklists to ensure more systematic evaluation of grant applications, explore longer-term support for investigators, and provide support for replication studies. In addition, NIH continues to monitor the situation through conversations with professional societies, journal editors, industry, academics, and other stakeholders in the research enterprise. At the same time, it is important to continue to support a research environment that values creativity, and any change in policy should avoid suppressing originality.

¹ see “Policy: NIH plans to enhance reproducibility” by Francis Collins and Lawrence Tabak recently pushed in the journal *Nature*.

5. How is the mission of the NIH different from private scientific foundations such as the Howard Hughes Medical Institution (HHMI)? Would it be fair to say that HHMI is willing to fund more high-risk, high-reward projects? Is the NIH also moving to fund more high risk, high reward projects? If so, why? What do you regard as the most important potential advantages and disadvantages?

The missions of the NIH and private scientific foundations, such as the Howard Hughes Medical Institute (HHMI), are more alike than different; both entities strive to make discoveries in the biomedical sciences, understand biological principles, train new scientists, and improve human health. Still, these organizations have different scopes and utilize distinct mechanisms to support their goals. For example, the NIH provides a wide variety of funding and training opportunities--from small to large research project grants and awards for centers, careers, and training. The HHMI has a narrower charge, principally funding a relatively small set of individual scientists at various stages of their careers who have already demonstrated great potential, and does not focus on specific projects.

Over the past few years, both NIH and NCI have developed several programs that emphasize the importance of funding projects that take larger risks for potentially greater rewards (e.g., the NIH Director's Pioneer Awards, the New Innovator Awards, the Early Independence Awards, the Transformative Research Awards, and the NCI's Provocative Questions initiative) or give more weight in the evaluation process to the quality of the investigator's past work than to proposed projects (e.g. the NCI's new Outstanding Investigator Award and the Pathway to Independence Award). Awards based on past performance are important because many agree that past performance is probably the best predictor of future productivity, and long term awards of this type help to stabilize a research environment. On the other hand, the NIH is often expected to follow up on scientific developments with projects that may be technically difficult but not highly imaginative or especially risky. The NCI's cancer genomics programs (such as TCGA) and its clinical trials programs belong to this category of activity---essential for a public institution but not for a private foundation.

In addition, the FY 2015 President's Budget request includes some specific initiatives related to innovative research. For example, the Budget proposes to invest \$100 million in a variety of High-Risk, High-Reward projects in the Institutes and Centers. In addition, the FY 2015 Budget includes \$30 million in new Common Fund projects designed to achieve breakthrough innovations in short timeframes and modeled after the research flexibilities utilized by the Defense Advanced Research Projects Agency (DARPA).

6. What is the value of studying rare diseases that only affect a very small portion of the human population? Would scientific discoveries made from understanding these diseases benefit our understanding of other more widespread diseases, like cancer and stroke? Please give some examples.

History has repeatedly shown that significant clinical advances come from studying a variety of areas that may not be obvious subjects for advancing human health, and our understanding of cancer and other common diseases has often been greatly expanded by the study of rare and diverse phenomena. While some cancer types may be common, many are quite rare, yet can offer valuable information about other cancer types. For example, research focused on a rare

cancer called retinoblastoma was critical for the eventual discovery of tumor suppressor genes, a class of genes that is affected in essentially every cancer. Similarly, work on neuroblastomas in rats led to the discovery of the oncogene, HER2, that is targeted by antibodies now widely used in the treatment of breast cancer. While there are only 200-300 cases of retinoblastoma and 700 cases of neuroblastoma diagnosed annually in the U.S., critical advances gained from the study of these two rare diseases has improved treatment and outcomes for countless numbers of cancer patients. Similar stories about the importance of studying rare diseases can be found in many fields of biomedical science.

7. It has been almost 43 years since President Nixon signed the National Cancer Act, in which he famously declared "the war on cancer." Where are we today in terms of progress for a cancer cure? Do we need to change our expectations from what biomedical research will produce?

When the National Cancer Act was passed and signed, we knew very little about cancer other than some important risk factors (e.g., tobacco use, radiation exposure, age, and [for some cancers] heredity) and some partly effective therapies (e.g., surgery in localized disease, chemotherapy for childhood leukemias, and radiotherapy for a few solid cancers). With the enormous growth in knowledge that was fueled by the increased funding for the NCI and the NIH generally, we have learned about many other features of cancer. These features indicate that cancer is not a single disease, but a variety of genetically heterogeneous disorders that arise by similar mechanisms (genetic and epigenetic) affecting many different cell types; that other important risk factors exist (e.g., certain viruses and other infectious agents, obesity, specific inherited genetic variants); and that novel approaches to therapy (targeted to mutant proteins or dependent on manipulation of the immune system) are possible.

All of this suggests that the goals and expectations of research need to be revised. We are unlikely to eliminate cancers entirely, since cancers can arise from mutations affecting normal genes in the course of normal events (e.g., DNA synthesis and cell division); it will be difficult to cure most cancers, given their heterogeneity and ability to develop resistance to therapy; more emphasis needs to be placed on reduced exposure to risk factors (e.g., through use of vaccines, control of obesity, and reduction in tobacco use) and the early detection and treatment of cancers, especially those that are likely to prove fatal. This new understanding and research focus are reflected in the gradual improvements in cancer mortality and in five-year survival data over the past couple of decades---largely attributable to improved therapy for some cancers, earlier detection of some, and major reductions in tobacco use. With continued support for efforts to characterize and understand individual cancers, it is likely that the scientific community will improve prevention strategies and design better therapies against most cancers over the coming decades. But a simple, single "cure" for all cancers is a remote possibility.

8. In July 2000, you testified before the House Committee on the Judiciary, Subcommittee on Courts and Intellectual Property (Hearing entitled: "Hearings on Gene Patents and Other Genomic Inventions"). You wrote that you were, "troubled by widespread tendencies to seek protection of intellectual property increasingly early in the process that ultimately leads to products of obvious commercial value, because such practices can have detrimental effects on science and its delivery of health benefits." While the Bayh-

Dole Act and scientific advances have helped generate a dynamic biotechnology industry, there have been changes that, in your words, "are not always consistent with the best interests of science." Could you please give us an update on your statement that you made at that time? What additional policy suggestions would you recommend at this time?

I still hold to the principle that intellectual property protection too early in the discovery process can impede progress, but I cannot comment on current practices without another study like the one we undertook in the late 1990's. My sense is that the situation has improved, that intellectual property constraints are less problematic, and that sharing is more common, albeit not ubiquitous. Appropriate intellectual property protection remains vital to industry, and at the same time data sharing is now as important to scientific progress as is sharing of materials and methods.

NCI continues to foster data sharing while maintaining appropriate intellectual property protection via its Technology Transfer Center (TTC), which provides services to support technology development activities for NCI and a number of other NIH Institutes and Centers. The NCI TTC works to establish collaborations among academia, federal laboratories, and industry, while utilizing patents, licenses, and Cooperative Research and Development Agreements (CRADAs) to encourage commercial development of technologies to benefit public health. Additionally, the Regulatory Affairs Branch within NCI's Cancer Therapy Evaluation Program fosters pharmaceutical collaboration in evaluating promising investigational agents, utilizing CRADAs, Material Transfer Agreements, and other relevant agreements to facilitate the sharing of data and materials.

9. Genome editing has recently made news with regards to HIV treatment to disable a gene in immune cells. In addition, new technologies like CRSIPR (Clustered Regularly Interspaced Short Palindromic Repeats) are being developed which will enable faster and easier methods to do genetic surgery and editing. Could you discuss the relevant policy issues we must take into account surrounding the technology of genetic editing? Are there any public policy implications of genetic editing that you are concerned about that should be addressed at this time?

The new methods you mention are leading to important advances in how we understand and treat disease. However, the use of gene editing in treatment of human disease does not raise any concerns that are fundamentally different from concerns about more traditional approaches to gene therapy: unintended effects on the human germ line, including unexpected changes that affect normal functions (e.g., of the immune system) or initiate cancers. Continued research and analysis, with oversight from groups like the RAC (the NIH Recombinant DNA Advisory Committee), are needed to understand these effects and thoroughly monitor their occurrence in future studies.

Rep. Elizabeth Esty

Member, Subcommittee on Research & Technology
 Committee on Science, Space & Technology
Questions for the Record (QFRs)

Subcommittee on Research & Technology

“Policies to Spur Innovative Medical Breakthroughs from Laboratories to Patients”

Thursday, July 17, 2014

QFR #1: This Committee often hears testimony about how the country is facing a shortage of workers with the appropriate STEM background. In this hearing, we focused particularly on interdisciplinary research and education. Could you please discuss the skills that are necessary for emerging interdisciplinary fields such as engineering biology? How do we balance interdisciplinary competence with disciplinary depth?

While there are concerns about the large size of the biomedical research workforce, producing a high level of competition for grants and jobs, there is also reason to be concerned about shortages of personnel with certain kinds of training, especially with the skills required for work on projects requiring multiple disciplines. There are several ways to deal with this issue: by building training programs that address more than one discipline (examples include programs in chemical biology, computational biology, cancer biology, and bioengineering); by providing specialized core facilities that allow investigators to harness skills that may not be available in their own laboratories; and by encouraging collaborations between laboratories with different skill sets through novel grant programs and collaborations between funding agencies. There is abundant evidence for the wider use of these approaches at many institutions and within the NIH intramural program. We would be pleased to provide examples of all three approaches upon request.

QFR #2: What is the role that NIH and centers like SynBERC can play in ensuring that our future researchers will have the background needed to be leaders in areas of science that are at the intersection of several fields including biology, physics, and engineering?

NIH and centers like Synberc recognize the benefit of bringing investigators with expertise in different scientific disciplines together under one roof or network. Synberc convenes leading scientists in the multidisciplinary field of synthetic biology at its Berkeley headquarters, as well as its university partner sites at the University of California San Francisco, Stanford, Harvard, and MIT. Similarly, interdisciplinary efforts like the Koch Institute for Integrative Cancer Research at MIT, an NCI-designated cancer center, utilize NCI support to bring together experts in fields ranging from systems biology, nanotechnology and engineering, to molecular genetics and immunology – fostering a collaborative and multidisciplinary environment to advance cancer research.

Synberc and the Koch Institute, as well as NIH and NCI, support training to develop researchers with diverse scientific backgrounds. Synberc also makes courses and curricula freely available for use at other institutions, and partners with middle schools, high schools, and K-12 science education organizations to provide educational programs and other resources. Examples of relevant NIH and NCI training opportunities include the NCI Nanotechnology Research Training Program and the NIH Mentored Quantitative Research Career Award (K25), which aims to increase the number of scientists trained to conduct high-quality interdisciplinary research.

Responses by Dr. Marc Tessier-Lavigne

Follow-up Questions and Answers

Dr. Marc Tessier-Lavigne, The Rockefeller University

Hearing of the Subcommittee on Research and Technology: "Policies to Spur Innovative Medical Breakthroughs from Laboratories to Patients"

July 17, 2014

Questions submitted by Rep. Larry Bucshon, Chairman,
Subcommittee on Research and Technology

1. How is the BRAIN initiative different from the human genome project of the 1990s? In what ways are the goals of the two programs different?
 - Both are large-scale, federally funded, collaborative science projects with ambitious goals.
 - However, the specific goals of each are quite different.
 - The specific objective of the HGP was much easier to define (though not necessarily to achieve): to determine the sequence of the 3 billion chemical base pairs that comprise the human genome and identify all of the genes therein.
 - The very broad charge of the BRAIN initiative, expressed by President Obama when he launched the project on April 2, 2014, is "to accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain to show how individual brain cells and complex neural circuits interact at the speed of thought."
 - The common feature is that both provide tools and information that can accelerate research by independent investigators, thus enabling the community of scientists.

2. Several articles in respected publications have commented on the issue of research reproducibility. It appears that the inability to reproduce scientific claims is becoming a serious problem. What are the causes behind this growing problem? What are your recommendations to prevent this problem from becoming more serious?
 - There are many reasons that independent replication of research findings is sometimes a challenge, and the articles cited in the question provide a more comprehensive analysis than is possible here.
 - Major causes include incomplete reporting of methods, inadequate or incorrect statistical analysis, and a bias toward publishing only positive results.
 - Another contributing factor in the life sciences is the use of reagents, such as cell lines and antibodies, which have inherent biological variability.
 - As well, some irreproducibility is actually the result of an incomplete understanding of all of the conditions influencing a result. This is especially the case in more complex experimentation such as behavior.
 - Finally, an important point is that intentional research misconduct, while an important area of focus, is believed to be a minor contributor.

- Given the broad array of factors contributing to this challenge, there is a diverse set of strategies for addressing it, including several highlighted in a recent editorial in Nature (“Reducing Our Irreproducibility,” April 2013).
3. The New York Times recently featured an article, written by a former Medtronic CEO, entitled: “Do Drug Companies Make Drugs, or Money?” The article stated that: “Research and development has proved to be less efficient at producing blockbusters than it was decades ago. But that doesn’t mean the goal should be to try to purge research and development budgets simply to pay out bigger short-term dividends.” As someone who once worked as the head of Genentech’s R&D efforts, what are your thoughts on this statement? The article also posits the following question: “Is the role of leading large pharmaceutical companies to discover lifesaving drugs or to make money for shareholders through financial engineering?” Can you share your perspective on this statement?
- [Note: The question incorrectly says the article was written by the former CEO of Medtronic. It was actually written by Andrew Ross Sorkin; the former Medtronic CEO is quoted in the article.]*
- The best biopharmaceutical companies strive for both medical and financial success by rigorously addressing unmet medical needs and poorly treated diseases.
 - Significant return on investment in the biopharmaceutical industry requires a robust research pipeline; therefore, widespread reduction in research funding is not a viable long-term strategy.
4. Could you discuss the benefits of genetic editing, including CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)? Are there any public policy implications of genetic editing that you are concerned about that need to be addressed at this time?
- CRISPR and other genetic editing technologies are exciting recent developments that facilitate genetic editing in cell lines and animal models, thereby accelerating research on many diseases.
 - As well, gene editing can be used for gene therapy, which aims to treat inherited genetic diseases by correcting the disease-causing mutations in the patients’ DNA.
 - The public policy implications of gene therapy are well known and have been widely discussed and debated since the emergence of the field of gene therapy over 30 years ago.

Question for the Record Submitted by Rep. Elizabeth Esty, Member, Subcommittee on Research and Technology, Committee on Science, Space & Technology

QFR #1: This Committee often hears testimony about how the country is facing a shortage of workers with the appropriate STEM background. In this hearing, we focused particularly on interdisciplinary research and education. Could you please discuss the

skills that are necessary for emerging interdisciplinary fields such as engineering biology? How do we balance interdisciplinary competence with disciplinary depth?

- The availability of highly trained scientists in a wide array of disciplines is needed to ensure the ongoing success of drug research and development.
- It is the nation's long-term investment in the basic biomedical sciences, as well as the "harder" sciences of physics, chemistry, math and computer science, that has led to the advanced instrumentation and data-processing tools that the drug discovery process now relies on.
- This broad investment across diverse disciplines over time is a prime reason the U.S. has become the undisputed leader in pharmaceutical breakthroughs.
- It is difficult to predict which intersections between disciplines will give rise to the next interdisciplinary field of drug-discovery research.
- Therefore, in addition to supporting disciplinary depth, our educational system must have mechanisms to facilitate cross-pollination and interactions among the disciplines. For example, graduates studies in the biomedical sciences should be given exposure to the applied side of their discipline, e.g., drug discovery.

Responses by Dr. Jay Keasling

HOUSE COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
SUBCOMMITTEE ON RESEARCH AND TECHNOLOGY

"Policies to Spur Innovative Medical Breakthroughs from Laboratories to Patients"

Dr. Jay Keasling, Professor, Department of Chemical & Biomedical Engineering, Professor, Department of Bioengineering, Director, Physical Biosciences Division, LBL, and Synthetic Biology Engineering Research Center, CEO, Joint BioEnergy Institute

Questions submitted by Rep. Larry Bucshon, Chairman, Subcommittee on Research and Technology

1. You recently predicted the convergence of synthetic biology and 3-D printing technologies to form synthetic life. Could you elaborate on this prediction? When do you foresee this becoming a reality? Do you believe public policymakers in Congress need to address the ethical ramifications of this?

There are a number of researchers that are attempting to bring these two technologies together. Most notably, Cambrian Genomics is working on a new form of laser printing that manufactures DNA. This technology employs traditional methods from sequencing to affix DNA fragments to a glass plate and grow them base by base. The problem with this method has always been accuracy, since the error rate for this type of synthesis is too high to reliably make the precise sequences we require. The novel aspect of the Cambrian Genomics approach comes from the fact that they make many thousands of copies of their sequence, ensuring that at least some proportion will have been made with the proper sequence. Each strand is affixed to a microscopic bead, then read to identify which beads hold strands with the sequence they're shooting for. Then, an automated laser scans the plate and blasts any beads with a desired sequence off of the plate and into a collector.

While the cost of reading DNA (sequencing) has plummeted thanks to next-generation sequencing, the cost of writing DNA (synthesis) remains high – about 50 cents per base pair of DNA. The amount of base pairs in the human genome would cost approximately \$1.5 billion to synthesize, and even *E. coli* (the simple workhorse microbe of many molecular biologists) has 4.5 million base pairs. DNA laser printer technology could lower this price by several orders of magnitude. The ability to print DNA could also enable bio-based manufacturing processes in remote locations, which could radically change the delivery and production of vaccines in developing nations, space travel, and many other fields. The technology could become available in the next five years, but more likely in the next 10-20 years.

DNA printing could make synthesis technology cheaply available to consumers. This would represent a boon to the burgeoning do-it-yourself biology (DIYbio) community. While there is no evidence that the DIYbio poses an immediate danger to the public or themselves, the ready availability of DNA printers would beg the question of how the government should ensure the safety and responsibility of do-it-yourself biologists.

2. This Subcommittee held a hearing last year entitled, "Prizes to Spur Innovation and Technology Breakthroughs". Could you suggest areas in the field of synthetic biology where it would be appropriate to sponsor innovation prizes? Why would prizes be a more appropriate vehicle for progress in these areas?

A \$1000 DNA printer might be one example of a potential synthetic biology-themed prize. Another might be a method to produce a flu vaccine in 36 hours. In general, such a prize ought to result in the use of synthetic biology to create a product or process that has practical use for real-world problems in areas like energy, health and environment. A prize for something like synthesizing the largest cell might demonstrate an important technical ability, but without a connection to real-world needs, such a contest might give the public the sense that synthetic biology is about performing tricks in a laboratory, rather than using biotechnology to improve human welfare.

I believe that prizes for specific products are especially appropriate vehicles because they tend to drive small innovators to develop products for consumers or industry that can in turn have exponential changes in existing practices and products. In addition, although only one contestant might win a prize, such contests may result in many different approaches in a relatively short time, and the winning approach might not always be the lasting approach.

In case the Subcommittee is not already aware, the synthetic biology company Gen9 has created a slightly different kind of contest called the G-Prize, in which contestants submit project ideas requiring extensive DNA synthesis. The winner(s) get one million base pairs synthesized for free in the pursuit of a creative and innovative synthetic biology project in industries such as pharmaceuticals, chemicals, biofuels and agriculture. Contest details are at <https://www.gen9bio.com/resources/get-free-genes/>. It might be possible for this Subcommittee to encourage other such approaches to spur innovation and partnership with private companies.

Responses by Dr. Craig Venter

"Policies to Spur Innovative Medical Breakthroughs from Laboratories to Patients"
 Dr. J. Craig Venter, Chairman & CEO, J. Craig Venter Institute

Questions submitted by Rep. Larry Bucshon, Chairman, Subcommittee on Research and Technology

1. What, if any, constructive criticisms do you have about the existing peer-review mechanism for awarding research grants?

The peer-review mechanism for awarding research grants has been in place for many years and on the whole has been an effective means for building the foundation for fundamental research that has led to many breakthroughs in our scientific understanding. However, the increasing pressure from reduced budgets, and the often biased view of study sections have made this mechanism ineffective. We suggest overhauling the peer-review mechanism to foster more innovation. Too often a track record of past awards is viewed more important than new, innovative ideas by researchers or research organizations without such a record. While past success is sometimes a good indicator of future success, it isn't the only sign pointing toward new discovery. We cannot discount the young researchers with new ideas who do not yet have track records. Nor can we discount the new idea that with some funding could take fields of research in whole new directions. While certainly the current system allows for a bit of this, it does not encourage and support enough of this. Industry and venture capitalist are shouldering this kind of innovation. I acknowledge that funding unproven researchers and their work is risky for government but I would argue this is exactly what our government should be rewarding and funding. DARPA is one example of this in our government but we need more DARPA-like agencies throughout government especially at the National Institutes of Health. Yes industry can help but we need our government pushing our researchers to seek new frontiers.

2. Where are we today regarding genomics medicine? Are we at the point at which we can sequence a person's genome and get his/her probability for a particular disease? Are the advances in sequencing human genomes "scalable", in terms of time (to sequence the genome) and the cost of doing it?

Genetics has long been a fundamental part of medical care for a very long time. For example, each time a patient has been asked about family history, the genes and thus a predisposition for a particular disease has been at the center of often critical health care decisions. However, the progress we have made over the last two decades in sequencing human genomes starting with the first draft human genome sequence (the efforts undertaken by the Federally funded human genome project and the private effort I led at Celera Genomics) to the more recent complete individual genomes (one of whom was mine) enables us to take a much closer look at the true molecular events that build the foundation of what eventually may have become "family history", and treat or prevent diseases that can be identified at the genome level. New sequencing platforms and computing and analysis technology allow us to sequence an entire human genome in a couple of days for less than \$10,000, extracting relevant information and applying it in certain areas of interest. This approach is fully scalable, affordable today and will fundamentally change clinical practice over the next ten years. However the speed and

accuracy is rapidly accelerating and the costs to do this work are dramatically decreasing. At our company, Human Longevity Inc., we already established the world's largest human sequencing facility with the capability of sequencing several hundred genomes each week, and continue to expand this throughput with the goal of reaching several thousand genome sequences on a weekly basis by the end of next year.

The challenge we are facing lies in the responsible translation of this knowledge into clinical practice. The creation of standards, including for example the definition of a medical or clinical grade genome, is paramount to guarantee a broad and successful implementation of genomic medicine.

3. One of the recommendations that you touch on in your testimony is that the government should establish "a new federal standard requiring whole human genome sequencing" that would benefit for-profit, non-profit, and government organizations and more importantly improve health care for Americans. What benefits do you foresee coming out of whole human genome sequencing? Could you further elaborate on what would be done by this federal standard for genome sequencing? This Committee had jurisdiction over voluntary standards-setting through the National Institute of Standards and Technology (NIST); is NIST the appropriate federal agency that you foresee developing such a standard?

Currently there is no quality or performance standard for generating a human genome sequence. If we neglect the development of such standards, we risk to eventually make clinical decisions that are based on poor quality data, inappropriate references and misleading interpretation of in particular population-based information that otherwise could effectively be used to prevent disease and better treat individual patients. A new federal standard for whole human genome sequencing can solve this issue.

"The technology to perform DNA sequencing has improved dramatically, and is now relatively inexpensive and rapid enough to consider mechanisms to accelerate the use of whole human genome sequencing as a standard feature of human clinical trials. Using whole genome sequencing will increase our understanding of the human genome and our ability to improve human health faster than less comprehensive genomic methods like SNP (Single Nucleotide Polymorphisms)-based methods like GWAS (Genome Wide Association Studies), or whole exome sequencing which focuses only on the protein-coding part of the genome.

The US government funds many human clinical trials, primarily through the NIH, and is in a position to encourage research scientists to transition from less comprehensive genomic methods to whole human genome sequencing through its existing competitive grant processes by making their preference for whole genome sequence clear and providing the necessary funding. There is a need to re-examine some of the current research conventions for representing whole human genome sequence data, and clarify some minimal quality standard. These will evolve rapidly though as technology continues to improve. One potentially useful approach would be have NIH work with NIST, and potentially other government agencies, to quickly obtain input from leading scientists about minimal quality standards for whole human genome sequencing for human clinical trials and publishing these for public comment. NIH, and other US

government agencies, could then use these standards in Requests for Applications (RFA) and scientific review and selection processes for human clinical trials."

4. I have heard the phrase "sending biology through the internet". Can you explain what that means in layman's terms?

Rather than having to ship biological specimens by FedEx or through the mail, today it is possible to sequence DNA in one location, send that digital DNA code through the internet, and then chemically synthesize that DNA at a completely separate location—resulting in an exact copy of the DNA at the first location.

Let me illustrate with an example that I mentioned in my written testimony. In March of 2013, there was an outbreak of a new viral strain of flu (called H7N9) in China. On March 31, the China Center for Disease Control and Prevention, announced the discovery of a cluster of cases in China and released the gene sequences of that new virus. Shortly thereafter, the U.S. Center for Disease Control (CDC) and the Biomedical Advanced Research and Development Authority (BARDA), requested that JCVI, SGI, and Novartis synthesize those genes posted on the internet in China, for use in for manufacturing a vaccine in the U.S. DNA synthesis began on April 1 at SGI in California, was completed the next day, and by April 7, a vaccine prepared from those genes was ready for testing in mice in a Novartis laboratory in Massachusetts.

Fortunately, that outbreak of H7N9 was quite contained. But if it had not been, the many weeks saved by "sending biology through the internet" and then immediately synthesizing the digital code into DNA could have saved many, many lives.

5. You recently predicted the convergence of synthetic biology and 3-D printing technologies to form synthetic life. Could you elaborate on this prediction? When do you foresee this becoming a reality? Do you believe public policymakers in Congress need to address the ethical ramifications of this?

In the example above, I talked about having the capability to produce a synthetic virus *today*. The ability to automate construction of more complex organisms, such as bacteria, will take more time.

In 2010, a team of researchers in JCVI's laboratories chemically synthesized the DNA "operating system" (that is, the chromosome) of a bacterial cell, bringing a new bacterial cell to life. But that last step has not yet been automated. I believe it will, but I cannot give you a date.

Public policymakers have already considered the ethical ramifications of this new technology. Shortly after we announced the creation of this first cell with a chemically synthesized chromosome, the House Committee on Energy and Commerce held a hearing on the topic and the Presidential Commission for the Study of Bioethical Issues undertook a six month study. That study, "New Directions: The Ethics of Synthetic Biology and Emerging Technologies", included a thorough review of both ethical concerns and potential benefits and risks to the public.

I believe that the ethical and societal implications of our research are as important as the science itself. My teams have been examining these aspects since 1999, thus I was able to

help inform both the House Committee and the Presidential Commission. I believe that both Congress and the Administration have done their job given where the field is today. But both I and the Presidential Commission recommend that policymakers continue to follow future developments.

6. This Subcommittee held a hearing last year entitled, “Prizes to Spur Innovation and Technology Breakthroughs”. Could you suggest areas in the field of synthetic biology where it would be appropriate to sponsor innovation prizes? Why would prizes be a more appropriate vehicle for progress in these areas?

Prior to the widespread availability of synthesized DNA, experiments that required manipulating DNA in the lab were slow, labor intensive, expensive, and limited in their reach. The success of synthetic biology to date has been largely due to the improved speed and flexibility of performing experiments using synthetic DNA, enabling a far faster design/build/test cycle than previously possible.

But progress in the field of synthetic biology is dependent on the speed, cost, and accuracy of producing large pieces of synthetic DNA, which though improving steadily, is still slower, more costly and more error prone than we would all like. I would be pleased to work with Jay Keasling and other synthetic biology colleagues on the specifications and rules for such a prize.

Questions submitted by Rep. Elizabeth Esty, Member, Subcommittee on Research & Technology Committee on Science, Space & Technology

1. This Committee often hears testimony about how the country is facing a shortage of workers with the appropriate STEM background. In this hearing, we focused particularly on interdisciplinary research and education. Could you please discuss the skills that are necessary for emerging interdisciplinary fields such as engineering biology? How do we balance interdisciplinary competence with disciplinary depth?

Perhaps the former notion a very broad “liberal arts” curriculum was just too broad, but it is also clear that training in just a single discipline is too narrow. Students interested in fields such as engineering biology obviously need deep underpinning in at least one aspect of both biology and a quantitative science such as math, statistics, computer science, or engineering. But just as important is the ability to observe and understand how each of several disciplines solves intellectual challenges. Physics, chemistry, sociology, linguistics, philosophy and many other disciplines have much to offer and depending on individual student interest, should be encouraged as part of an interdisciplinary education.

Appendix II

ADDITIONAL MATERIAL FOR THE RECORD

STATEMENT SUBMITTED BY RANKING MEMBER EDDIE BERNICE JOHNSON

OPENING STATEMENT

Ranking Member Eddie Bernice Johnson
Committee on Science, Space, and Technology

Research & Technology Subcommittee Hearing
“Policies to Spur Innovative Medical Breakthroughs from Laboratories to Patients”

July 17, 2014

Thank you, Mr. Chairman for holding this hearing. This morning we are talking about interdisciplinary research and federal policies to spur medical innovation. Encouraging innovative medical breakthroughs starts with investing in fundamental research, including in emerging interdisciplinary areas.

Today we will hear from some of the witnesses about engineering biology—which is research at the intersection of biology, the physical sciences, information technology, and engineering. This exciting new area will potentially allow researchers to create biological systems that do not occur naturally and to re-engineer existing biological systems to perform novel tasks. This powerful new research area has the potential to address many of our most serious societal challenges.

For example, in healthcare, this field could lead to new therapies that are tailored specifically to individuals based on their genetic information. In energy, this field could lead to the use of microorganisms such as bacteria to produce fuel. Many other potential applications of engineering biology, including for agriculture, chemicals, and manufacturing, could save lives and lead to significant economic growth.

Given this promise, I have been working on a draft bill, which I anticipate introducing in the near future, that would establish a framework for greater coordination of federal investments in engineering biology and lead to a national strategy for these investments. The bill would also focus on expanding public-private partnerships and on education and training for the next generation of engineering biology researchers.

Additionally, my bill will ensure that we address any potential ethical, legal, environmental, and societal issues associated with engineering biology. It will also ensure that public engagement and outreach are an integral part of this research initiative.

The goal of this legislation is to ensure that the United States remains competitive in this critical area of science and technology. If we do not make the necessary investments, we will lose our leadership position in engineering biology.

We are already seeing other countries make significant progress. The EU and others are making the necessary investments, working on coordinated strategies across their research infrastructure, and developing action plans to execute that strategy.

Right now, we are still lead in engineering biology, but we must continue our work to ensure that we do not cede our leadership position. This field has too much potential to grow our economy, create jobs, and improve our quality of life. Even though we are in an increasingly interconnected world, it is important to do all we can to promote innovation and job creation here at home.

I am hopeful that we can work together across the aisle to ensure that the United States remains a leader in engineering biology.

I want to thank the witnesses for being here today. Thank you, Mr. Chairman and I yield back the balance of my time.

LETTER SUBMITTED BY SUBCOMMITTEE ON RESEARCH AND TECHNOLOGY
CHAIRMAN LARRY BUCSHON

ERIC SWALWELL
18TH DISTRICT, CALIFORNIA
ASSISTANT DEMOCRATIC WHIP
COMMITTEE ON SCIENCE,
SPACE, AND TECHNOLOGY
• RANKING MEMBER—SUBCOMMITTEE
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July 24, 2014

The Honorable Larry Bucshon
Chairman
Committee on Science, Space and
Technology
Subcommittee on Research and Technology
U.S. House of Representatives
2318 Rayburn House Office Building
Washington, DC 20515

The Honorable Daniel Lipinski
Ranking Member
Committee on Science, Space and
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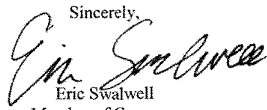
Chairman Bucshon and Ranking Member Lipinski:

I write to commend you on your July 17, 2014 hearing entitled “Policies to Spur Innovative Medical Breakthroughs from Laboratories to Patients.” Holding such a hearing provides an opportunity for a productive conversation on the importance of biomedical research.

I represent the Eastern San Francisco Bay area and we understand that to succeed you have to take big risks. Few things highlight the big gains that can be realized from big risks like the breakthroughs in medical technologies and treatments that save lives and reduce health care costs. But, innovations in science and medicine do not happen accidentally. They require an investment of private and public funds and a commitment to striving for the next breakthrough.

Public and private investment in science has benefited the American people and the world for decades. Not only does investment in research and development help us treat and prevent diseases, give our troops better equipment, and point us towards cleaner, safer sources of energy, it also creates skilled, private-sector jobs right here in America.

I look forward to continuing to work with you and the rest of our colleagues on the House Committee on Science, Space and Technology to promote the research and development that will continue to move our country forward.

Sincerely,

Eric Swalwell
Member of Congress

ARTICLE SUBMITTED BY REPRESENTATIVE DANA ROHRBACHER

Do Drug Companies Make Drugs, or Money?

The New York Times, June 2, 2014

DealBook M&A

By ANDREW ROSS SORKIN

June 2, 2014 9:05 pm Comment

"I just want to emphasize that this is an industry where it is composed of really great people, working to do good things for patients, for doctors and actually for society, and when I look at our employees, there is sort of a noble purpose to working in the pharmaceutical industry."

That was Mike Pearson, the chief executive of Valeant Pharmaceuticals International, waxing poetically last week about the virtues of his company. He was doing so as he was trying to sell shareholders of Allergan, the maker of Botox, on his company's \$53 billion takeover bid.

Mr. Pearson may have wrapped himself in the promise of the pharmaceutical industry's ability to deliver lifesaving breakthroughs, but there's a not-so-small problem with his self-righteous declaration: Of virtually every big drug company, Mr. Pearson's may very well be among the least innovative.

To the extent Mr. Pearson has succeeded over the years, he has done so largely by sharply cutting research and development budgets, arbitraging tax domiciles — Valeant left the United States for Canada's lower tax rates in 2010 by merging with Biovail — and buying rivals so he can cut their costs, too, while they take advantage of his lower tax rate.

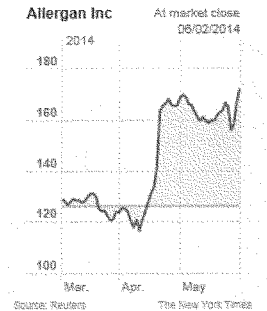
Bill George, a professor of management practice at Harvard Business School and the former chairman and chief executive of Medtronic, recently asked a provocative question: "Is the role of leading large pharmaceutical companies to discover lifesaving drugs or to make money for shareholders through financial engineering?"

Mr. George asked the question in the context of Pfizer's recent failed bid for AstraZeneca, but he could have been talking about Valeant.

Mr. Pearson's Valeant famously teamed up with Bill Ackman, the activist investor who runs Pershing Square Capital Management, to buy nearly 10 percent of Allergan's shares through a complicated transaction that some suggested was tantamount to front-running. It hoped to use that leverage to persuade Allergan's shareholders to accept Valeant's bid, which it has now raised several times.

Over the last several weeks, Mr. Pearson and Mr. Ackman have engaged in all sorts of criticism and name-calling of Allergan and its chairman and chief executive, David E. I. Pyott.

Mr. Ackman called Mr. Pyott conflicted and said he "appears to be motivated more by personal animus than by what is in the best interest of Allergan shareholders."



[That kind of language may just be part of the game, but it is particularly curious because Allergan isn't one of those horribly managed businesses that are often the targets of such vitriol. Here's what the investment firm Sterne Agee said in its recent research report: "The Allergan executive team is one of the best and most shareholder-focused in the pharmaceutical industry." The numbers tell the story: Allergan's stock is up 290 percent over the last five years.

And so what we're left with isn't a tale about a brilliantly innovative drug company trying to buy a mismanaged fixer-upper; it's quite the opposite. Valeant, desperate for ways to increase its revenue, needs a cash cow to milk until it can find the next one.

"Allergan spends 17 percent of its revenue on research and development, compared to Valeant's 3 percent, and Valeant has said it plans to cut around 28,000 jobs in the merger. We do not believe that this is the sort of economic activity that policy makers should be actively encouraging in their rule-making (or foot-dragging)," Martin Lipton, the co-founder of Wachtell, Lipton, Rosen & Katz, which has long railed against the short-term nature of activist investing, wrote in a note to clients. Given his views, it shouldn't come as a surprise that Mr. Pyott hired Mr. Lipton's firm to help defend against Valeant.

In case there is any question about Valeant's slash-and-burn strategy, here is Mr. Pearson in his own words from last week on the value of research and development: "There has been lots and lots of reports, independent reports, talking about how R&D, on average is no longer productive. I think most people accept that. So it is begging for a new model, and that is hopefully what we have come up with."

Mr. Pearson isn't completely wrong: Research and development has proved to be less efficient at producing blockbusters than it was decades ago. But that doesn't mean the goal should be to try to purge research and development budgets simply to pay out bigger short-term dividends.

And here is Mr. Pearson on his tax-dodging strategy: "As I think maybe you are aware, we were able to get a corporate tax structure which took our effective tax rate from 36 percent over all to what was actually 3.1 percent, which we hope to continue to work on and move lower." How much lower can it go?

Mr. Ackman, who has a terrific investment performance record and a mixed activist record — he practically destroyed J. C. Penney while doing miraculous work to resuscitate General Growth Properties — has been encouraging Mr. Pearson to increase his offer to induce Allergan to the negotiating table. On Friday, he announced a new twist that he implied should make it clear this is no short-term play for him.

“Early this morning, I called Mike and offered to give up \$600 million of value to the other Allergan shareholders and exchange our shares for Valeant stock if Valeant were prepared to increase its offer to the other Allergan shareholders,” Mr. Ackman said in a statement. “We believe that our gesture to the other Allergan owners makes an extraordinarily strong statement about our belief in the long-term value of this highly strategic business combination.”

What was missing from Mr. Ackman’s statement? He didn’t say exactly how long he planned to be a Valeant shareholder.

Of course, the saddest part of this battle between Valeant and Allergan is you never really know if the target is trying to defend itself against a deal it knows to be destructive or if it is just playing its well-rehearsed part in a negotiating dance to obtain a higher price. But if Allergan sells, you know the outcome.