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Committee on Energy and Commerce, Subcommittee on Health

Hearing Titled: "The Future of Biomedicine: Translating Biomedical Research into Personalized Health Care."

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Good morning, Chairwoman Eshoo, Ranking Member Guthrie and members of the Subcommittee. I am honored to have the opportunity to appear before you on behalf of the Stanford University School of Medicine and share my perspectives on the future of biomedicine in the United States. I'd like to express my gratitude to Rep. Eshoo for her years of support of Stanford School of Medicine and her visionary leadership and advocacy for basic science research. I also thank this committee and Congress for your longstanding, bipartisan support of biomedical research, demonstrated by significant investments in the National Institutes of Health and other federal science agencies. It is because of federal support for basic research that scientists across the country are building knowledge that saves lives, catches disease in its most treatable stages, and brings new hope to millions of Americans struggling with illness.

Today, we — as a nation and a global community — are enjoying an unprecedented era in biomedicine, one that is not only rapidly enabling people to live longer, healthier lives but also is fundamentally reshaping our future. At the heart of this progress are scientists engaged in basic research. Their discoveries provide the foundational knowledge upon which all novel therapeutics, interventions, and diagnostics are built.

Exemplifying Basic Science's Potential

In labs at Stanford and across the country, researchers pursue new scientific knowledge often without understanding precisely how their discovery may ultimately help advance the practice of medicine. Yet, time and again, this pursuit of knowledge toward deeper understanding has produced stunning medical advances, generated entirely new fields of research, and made the unimaginable possible. The immense progress we have made against cancer exemplifies the power and possibility of basic research.

Between 1999 and 2019, the rate of cancer deaths in the United States fell from 200.8 per 100,000 people to 146.2. This 27.2 percent reduction is a product of decades of advances in labs worldwide, including those on Stanford's campus. The rapid development of new knowledge and innovative technologies makes me optimistic that we will continue to make gains – and one day cure cancers altogether.

Ronald Levy, Stanford professor of oncology, has been at the forefront of efforts to find new, more effective treatments to cancer. This includes his NIH-supported research that showed the promise of injecting two immune-stimulating agents directly into solid tumors. In a mouse study, this therapy eliminated all traces of cancer – including distant, untreated metastases – and it has shown efficacy against several cancer subtypes.

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Dr. Levy's research could one day lead to a rapid and relatively inexpensive cancer therapy where patients receive targeted applications requiring a very small amount of active agents. Significantly, this intervention appears unlikely to cause the adverse effects associated with non-targeted or body-wide, immune stimulation.

While promising, activating the immune system at the site of a tumor presented a significant challenge in practice: delivering therapy to cancers in locations in the body that are not easily accessible. Building on his groundbreaking work, Dr. Levy and his Stanford research colleagues, including Drs. Jennifer Cochran and Carolyn Bertozzi, have found a potential solution. Enabled by NIH grants, they have developed a synthetic molecule that combines a tumor-targeting agent with another molecule to start immune activation. A paper published last month in the peer-reviewed scientific journal *Cell Chemical Biology* showed that three doses of this new immunotherapy prolonged survival in six of nine laboratory mice modeling an aggressive form of breast cancer. Of those six, half appeared to be cured of their cancer over the course of the months-long study.

The work of Dr. Levy and his colleagues exemplifies how fundamental discoveries are creating opportunities for better care. Yet, Dr. Levy recognizes that his work is not the product of only his own ingenuity and effort. He is the first to credit the groundbreaking work in basic science by those who came before him and developed knowledge that created pathways for him to make further advances.

In 1975, two University of Cambridge scientists created hybridomas, essentially hybrid cells that consist of an antibody-making cell attached to a cancer cell. Dr. Levy saw the therapeutic potential of the monoclonal antibodies produced by the hybridomas and began experimenting. He found that injecting monoclonal antibodies targeting lymphoma cells from mouse hybridoma cells into humans eliminated the cancer cells but not the normal cells.

By 1981, Dr. Levy's team had cured their first patient with B-cell lymphoma, and four years later they launched IDEC Pharmaceuticals to make custom antibodies for individual patients. (IDEC Pharmaceuticals merged with the biotechnology company Biogen in 2003.) The company has since developed Rituxan, which in 1997 became the first commercial antibody to receive FDA approval to treat cancer. By 2009, Rituxan was recommended for treating nearly all lymphoma patients and had been administered to 1 million people. Beyond its efficacy, Rituxan demonstrates fewer side effects than conventional cancer treatments and does not permanently damage the immune system. The drug also has applications in the treatment autoimmune diseases such as rheumatoid arthritis.

Dr. Levy's career journey illustrates how discoveries in basic science have made it possible to diminish the impact of cancer, which remains the second leading cause of death in the United States. Each discovery in basic science creates an opportunity to further extend knowledge, providing dividends for years and decades following an initial discovery.

An Urgent and Critical Need for Support

The United States has long been a leader in basic science research thanks largely to NIH funding, and I believe that Dr. Levy's career shows that supporting basic science is of the utmost importance. Through discovery-focused research, we continue the legacy of generations of scientists to allow the citizens of tomorrow the opportunity to experience better and healthier lives.

As another example, consider the vaccines, including mRNA-based vaccines, that have proved so effective against COVID-19. Beyond the hundreds of thousands of lives saved, these vaccines will help blunt the financial burden of the pandemic that some economists estimate will reach a staggering $16 trillion. Yet, had it not been for the decades of basic research that preceded this devastating pandemic, we would be in an even more challenging position.

Beyond COVID-19, Alzheimer's disease, for example, is placing an extraordinary burden on Americans as well as the national budget, with effects that are projected to worsen significantly. In 2021, treatment for this neurodegenerative disease will cost the United States economy $355 billion. By 2050, without the rollout of an innovative therapy, this total is expected to exceed $1 trillion.

Scientists across the country are making significant progress in basic research that will likely contribute to the battle against Alzheimer's disease. This year, Katrin Andreasson, MD, professor of neurology and neurological sciences at Stanford, identified a key factor in mental aging, illuminating possibilities for how mental aging could be prevented or reversed. Her NIH-supported work showed that myeloid cells, a type of immune cell, can cause inflammation in the brain as people age. Biologists have long theorized that slowing this inflammation could delay the onset of Alzheimer's disease, as well as other age-associated conditions like heart disease, cancer, and other diseases.

The promise of Dr. Andreasson's and Dr. Levy's work demonstrates the need for continued, strong federal support for basic research. As discoveries reveal answers to scientific mysteries, they also open new fields of study, allowing a greater understanding of human biology and how to better prevent or treat disease.

Consider the example of Mark Davis, professor of microbiology and immunology at Stanford School of Medicine.

In 1980, Dr. Davis, who had recently earned his PhD, set out to unravel one of the immune system's greatest mysteries – understanding the mechanism for how immune cells are able to distinguish foreign entities in the body. His curiosity, tenacity, and skill led him to identify the two T-cell receptor genes that enable human immune systems to detect and attack cancer cells and pathogens. These foreign pathogens include the virus that causes COVID-19.

With colleagues, he built upon these earlier discoveries, learning about the biochemical and functional properties of T cells. Davis's work has ushered in a new era of science in which scientists routinely engineer T cells to better understand how the immune system works and deploy engineered T cells to attack disease.

More than 40 years later, Dr. Davis's discovery continues to serve as the foundation of critical medical discoveries. This summer, he published a study showing that COVID-19 patients with milder symptoms were more likely to have signs of prior infection by similar, less serious coronaviruses than SARS-CoV-2. These findings, made possible by an NIH grant, could potentially be used to predict who will develop the more severe symptoms of COVID-19, and potentially help prioritize interventions. I am confident that the impact of Dr. Davis's work will continue to ripple across the biomedical landscape for decades to come.

Leading a New Era of Biomedicine

For years, long before COVID-19, Stanford Medicine has realized the opportunities created by the explosion of health data, rapid advances in artificial intelligence and machine learning, and other innovative technologies – all the result of discoveries in basic science. The opportunities unlocked by these advances form the foundation of Stanford Medicine's Precision Health vision. Through Precision Health, Stanford Medicine is fundamentally transforming our current system of sick care, addressing problems as they arise, to true health care, which takes a holistic view of treatment and prevention.

Precision medicine, the idea of tailoring interventions to treat individual patients, has become commonplace across health systems. In contrast, Precision Health is a shift to more proactive patient care. In other words, Precision Health doesn't simply treat patients, it is an approach to predict, prevent, and cure disease in a precise manner. Perhaps the greatest focus of Precision Health is on social determinants of health — the social, behavioral, and environmental factors that underlie approximately 70 percent of health issues and adverse outcomes. By addressing these factors, we can predict or prevent many more diseases before more significant, expensive, and invasive interventions are required. The long-term vision for Precision Health will be realized when we see a decreased reliance on reactive precision medicine interventions.

One emerging Stanford Medicine innovation, among many, exemplifies the power and potential of Precision Health interventions to combat depression. Known as SAINT (Stanford Accelerated Intelligent Neuromodulation Therapy), this experimental treatment uses a magnetic coil to stimulate underactive parts of the brain in people with clinical depression. In October, the American Journal of Psychiatry published the results from SAINT's latest clinical trial in which 80 percent of study participants went into remission.

Research studies show that the risk of a suicide attempt is particularly high in the months following discharge from a psychiatric facility for patients who have previously attempted suicide. Two larger trials are in progress to validate the safety and efficacy of SAINT, including one funded by the NIH. Though this innovation has immediate impacts to aid people suffering from depression, it also has the potential to serve as a rapid anti-depressant that contributes to the prevention of further suicide attempts.

Beyond the promise of SAINT, Precision Health is already having a profound impact on society. I'm proud that Stanford Medicine has shared our vision for proactive care and expertise with the All of Us Research Program. This NIH program seeks to speed up medical research by recruiting one million U.S. citizens to share key data about their health, habits, and environment.

We joined the All of Us program because it aligns perfectly with Stanford Medicine's longstanding mission to increase participation in clinical and biomedical research within vulnerable populations, including the LGBTQ+ community. We are optimistic that researchers from across the country will use the data we gather to better understand the social determinants of health. And through this better understanding, we will usher in innovative ways to treat and, most importantly, prevent disease.

While basic research remains the bedrock of innovation, translational research is also critical to our goals of improving human health. At Stanford Medicine, we are encouraged by the promise of a model that supports basic science and the translation of discovery through the creation of an Advanced Research Projects Agency for Health (ARPA-H). Legislative efforts to fund and establish ARPA-H, such as Chairwoman Eshoo's recently

introduced authorizing legislation, recognize the critical importance of our country's biomedical enterprise and reflects our aspirations to move discoveries from lab bench to bedside.

I'm proud that we at Stanford Medicine have a mini ARPA-H model of sorts. Our Innovative Medicines Accelerator (IMA) seeks to expand our knowledge of human biology and accelerate the translation of basic research discoveries into novel therapies and diagnostics. We began the IMA to overcome an obstacle that all academic medical centers face: the valley of death in which high-potential ideas developed in labs fail to progress to clinical testing.

Stanford Medicine established the IMA to bridge that gap. This includes providing Stanford researchers with the resources they need to move from the idea stage to a therapeutic candidate that can be tested in animals. Through the IMA, we have also established alliances with government, industry, and nonprofits to benefit from their translational expertise. Additionally, the IMA offers an expanded drug prototyping unit, a biobank that houses samples and data, and an off-site "freezer farm" to lessen the risk of sample destruction. It also includes a seed fund that supports promising research and facilitates the identification and validation of therapeutic and diagnostic targets.

Though only recently formed, the IMA has already had a significant impact. Originally designed to aid the development of medicines for diseases such as cancer and rare disorders, the IMA pivoted early in the pandemic. It constructed an expanded biosafety level 3 facility, awarded research grants, issued a follow-on request for proposals for vaccine prototypes, built an outpatient COVID-19 clinical and translational research unit, supported two trials on repurposed drugs, and initiated two industry-sponsored trials. This pivot has enabled Stanford Medicine faculty to more efficiently generate and test new medicines that will not only help society overcome the pandemic but that pave the way for breakthroughs in other conditions.

Investing in Tomorrow's Biomedical Leaders

In addition to highlighting what the U.S. is funding, it's critically important to look at who the U.S. is funding. The United States needs to continue to cultivate biomedical talent. The pandemic seems to have inspired young people to enter biomedicine. A recent global survey found that 45 percent of college students are considering a career in health and science — potentially widening and diversifying our biomedical talent pipeline.

Though this influx of talent is promising, we must collectively work to blunt the disproportionate impact that COVID-19 has had on early-career investigators. These scientists have had to pause research, respond to the urgent patient care crisis, and have faced hiring freezes at their research universities. I commend Rep. Eshoo, Rep. Upton, Rep. DeGette, Rep. Johnson, Rep. Gonzalez and the 170 other Members of Congress for co-sponsoring the RISE Act. Their recognition of the pandemic's impact in this field, acknowledgment of the catastrophic long-term impact it could have, and initiative to provide funding and support for research impacted by the pandemic will help to ensure early-career scientists can continue promising studies.

Even before COVID-19, researchers at all levels have faced significant challenges in receiving NIH funding. Since 2000, NIH applications have doubled, but the success rate of those applications declined from 32 percent to 21 percent. The issue isn't one of quantity subverting quality. Even research proposals that federal agencies rate as excellent are often not funded from lack of resources. It is disheartening to think about the lost potential of quality research projects that don't get off the ground for lack of funding. The significant funding appropriated

to NIH over the years has provided many opportunities for researchers across the nation, but by further increasing resources, the federal government can cultivate an even more fertile landscape for researchers at all career levels and for the thousands more aspiring to enter this field.

Addressing Health Equity

At Stanford Medicine, we recognize that diversity of thought and background are critical to enhancing our nation's health innovation landscape. We need scientists who reflect the diversity of our country and who are empowered to pursue their passions.

This acknowledgment of underrepresentation in biomedicine has fueled Stanford Medicine's commitment to cultivating a more diverse pipeline of physicians and scientists, educating all students about the scourge of health inequity, and identifying ways to address the health issues of underserved communities around the Bay Area.

As part of this, the Stanford School of Medicine has established funding models that have eliminated debt for MD students who qualify for financial aid and provide full support to graduate students pursuing training in the biosciences.

In addition to encouraging students to follow their curiosity and creative interests, this funding has diversified our classes. Our 2020 class of matriculating medical students was the most diverse in Stanford's history, with 38 percent coming from groups underrepresented in medicine, an increase from 26 percent in 2019. Among the 2020 class of PhD students, 29 percent were underrepresented in medicine, up from 22 percent the previous year.

I'm also proud of how Stanford Medicine has supported the Biosciences HBCU Initiative. We have developed partnerships with 16 historically black colleges and universities, including 10 of U.S. News and World Report's top 25. Additionally, the Health Resources and Services Administration-funded Stanford Hispanic Center of Excellence has endeavored to increase the number of Hispanic students and faculty participating in Hispanic health research, among other efforts to improve diversity, equity, and inclusion.

These efforts reflect Stanford's commitment to addressing a distressing fact: though the United States has stood at the forefront of biomedical innovation, not all have experienced it equally. Some have benefitted only modestly from the breakthroughs of the past 30 years, and some have not at all.

- Black Americans have higher rates of death than white Americans at almost every point in their lifespan. In 2019, for example, 355,000 Black Americans died, and approximately 20 percent of those deaths occurred earlier than the expected rate for white Americans.
- In 2019, Black infants had a mortality rate more than two times the level of white infants.
- Two-thirds of children of Puerto Rican descent don't respond to the drugs used in asthma inhalers, hammering home the need for greater diversity in research, from basic science to translational and through to clinical studies.

These few of many examples of health inequality underscore the importance of having diversity at all levels of our nation's labs and clinics. Yet, despite admirable progress by the NIH over the past decade, scientists from

underrepresented groups still face more significant barriers to receiving federal funding. For example, the NIH noted in 2019 that success rates for Black researchers applying for Type 1 R01-Equivalent grants were approximately 7 percentage points lower than white applicants.

Though the COVID-19 pandemic may only serve to deepen these divides, its disproportionate impact on communities of color has highlighted areas where diverse representation could lead to more equitable outcomes, such as the importance of diversity in clinical trials. The New York Times reported in September 2020 that Black Americans make up just 5 percent of clinical trial participants, despite being 13 percent of the U.S. population. The broadly diverse clinical trials that helped validate the COVID-19 vaccines were a splendid example of how we can do better for clinical research in general, and we must continue to do more.

At Stanford Medicine, we are striving to increase representation of underrepresented groups in clinical trials to ensure that newly developed interventions are relevant to the diverse populations we serve. For example, our Stanford Cancer Institute, a National Cancer Institute Designated Comprehensive Cancer Center, continues to work to broaden participation in clinical trials by conducting community engagement activities in the Bay Area. Through these efforts, we are gaining a better understanding of what local communities know about these potentially life-saving interventions – and their attitudes toward them.

Strengthening a Strength

Because of our vast network of academic medical centers, ongoing support from the federal government, and a diverse population, the United States is uniquely poised to continue to lead the scientific revolution. Despite the advances I've discussed, of the approximately 10,000 known diseases, we have just 500 treatments. This underscores the vast need — and potential — of the impact of basic science research in the future.

For decades, the federal government has provided bipartisan support for investments in basic research through the NIH. As an American citizen and clinician-scientist, I am incredibly grateful for this ongoing support. This sustained effort has catalyzed discoveries that have transformed the world and maintained U.S. preeminence in science and technology. However, as competing economies around the world increase their investments in biomedical research, remaining at the forefront requires continued investment in basic science at or exceeding current levels.

Through continued strong increases in funding for basic science research, the federal government will help ensure that all people — regardless of race, ethnicity, or sex — benefit from the truly transformative advances propelling biomedicine today. I hope you agree that this is an urgent issue for United States citizens and for our country's future.