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SUBCOMMITTEE OF LABOR, HEALTH, AND HUMAN SERVICES
COMMITTEE ON APPROPRIATIONS
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Chairman Rehberg, Ranking Member DeLauro, and members of the subcommittee, thank you for the opportunity to provide my perspectives on the role the National Institutes of Health (NIH) can and should play in the basic research versus translational research spectrum. I am here as policy advisor of the American Society for Biochemistry and Molecular Biology (ASBMB) to advocate for an increase in the funding of basic research that provides new knowledge in biology and disease critical for discovery of important new drugs and vaccines.

I was trained as a physician at Columbia University, College of Physicians and Surgeons. After residency at Massachusetts General Hospital I spent 10 years at NIH where I took care of patients with heart problems and did biochemical research. I then spent nine years at Washington University School of Medicine as Chairman of Biochemistry where I taught medical and graduate students and did basic research. I joined Merck as the head of research in 1975---a job I held for 10 years prior to becoming Chairman and CEO of the company for an additional nine years. Since my retirement from Merck at age 65 (Board policy at Merck) I have chaired the University of Pennsylvania and two biotech companies, Regeneron Pharmaceuticals, Inc. and Theravance. I am currently chairman of Regeneron and the Columbia University Medical Center Board of Visitors. I give these details to indicate that I have experience in clinical work, basic research, drug discovery and development and pharmaceutical and biotech company leadership. I will give an example that illustrates my views on the drug discovery process, and I will conclude with my opinions as to what is needed for future improvements in health that will result from discovery of important new drugs and vaccines.

The Cholesterol Hypothesis. This hypothesis, prevalent in the 1950's through 1980's, suggesting that high blood cholesterol can cause heart attacks, was based on the finding of cholesterol in plaques that blocked the coronary arteries in people dying of heart attacks, animal experiments, and human epidemiological studies that showed that populations with high blood cholesterol had high incidence of death from heart attacks while those with low blood cholesterol had a much lower incidence of heart attack. During this period, basic research in academia - that led to numerous Nobel Prizes - uncovered the complicated mechanisms used by the human body to make cholesterol and control cholesterol levels in the blood. There are about 20 sequential enzymatic reactions that are required in the formation of cholesterol but one of these is uniquely critical in controlling the rate of cholesterol formation.

This important knowledge caused many industry laboratories to focus on this enzyme with the idea that blocking this reaction might reduce blood cholesterol.

Akira Endo at Sankyo Company in Japan won this race when he discovered mevastatin, the first inhibitor of this enzyme, and this drug was shown to lower blood cholesterol in animals and humans. Alfred Alberts at Merck followed with the discovery of another inhibitor of this enzyme, lovastatin (Mevacor). Both mevastatin and lovastatin were being studied in human clinical studies when the studies with mevastatin were stopped abruptly. Sankyo Company refused to give information as to why the studies were stopped, but there were rumors that the drug was found to cause tumors in animals. The possibility that all inhibitors of this enzyme might cause tumors caused Merck to stop immediately all human studies for two years while extensive animal studies showed that lovastatin was safe. Human studies were then resumed and these studies showed that lovastatin safely reduced blood cholesterol and specifically LDL-cholesterol, the bad kind of blood cholesterol. The FDA approved use of lovastatin in patients with coronary heart disease and high blood cholesterol in 1987. Some doctors believed the cholesterol hypothesis and began using the drug; others did not.

Merck Research Laboratories followed with a second statin, simvastatin (Zocor), a drug somewhat more potent in reducing blood cholesterol. In a large outcomes study in patients with coronary heart disease and high blood cholesterol in Scandinavia covering 5.5 years simvastatin was shown to reduce overall mortality by 30%, death from heart attacks by 43% and strokes by 30%. This single experiment, reported in 1993, changed the cholesterol hypothesis to fact and started the statin revolution in treatment of heart disease.

The components of this overall discovery and development story are obvious: many years of basic research in academia (funded overwhelmingly by the NIH) to produce the knowledge of cholesterol formation followed by many years of industry research to produce the statins. There were drugs being used to lower cholesterol prior to the statins, but they were either not safe or effective enough to be broadly used. These earlier drugs were not developed based on the biochemical understanding that came later. But has this paradigm for drug discovery changed? During this past decade a new approach to lower blood cholesterol

and LDL-cholesterol even more dramatically is being pursued. This approach is based on knowledge emanating from academia that another enzyme complex, PCSK9, is involved in cholesterol regulation in humans, and several large and small companies are racing to determine whether blocking PCSK9 will safely reduce LDL-cholesterol beyond the levels attained with the statins. The statins have improved cardiac health over several decades. Will these new drugs improve on the statin accomplishments? Stay tuned. (I must admit that scientists at Regeneron appear to be in the lead). When basic knowledge is available to suggest that attacking a specific target molecule in humans or a pathogen can treat or prevent a disease, exciting things happen---fast.

Most of the important drugs and vaccines over the past 30 years have had a similar history: basic knowledge from academia, translational (or applied) research in small and large companies causing extraordinary improvements in health. We have seen major improvements in osteoporosis, organ transplants due to better immune suppression to prevent rejection, diabetes to reduce its complications, rheumatoid arthritis with TNF blockers, antidepressants, drugs for schizophrenia, HIV infection, some dramatic treatments in a few cancers, peptic ulcer disease, migraine headaches, wet age-related macular degeneration, etc. The list is long.

But much remains to be done. While we have seen important reductions in cardiovascular deaths, people still die of heart disease and we need new information there. We are seeing a blossoming of new information in neurosciences, but we need even more in order to discover targets for treating Parkinson's Disease, Alzheimer's Disease, better antidepressants and drugs for bipolar disease, amyotrophic lateral sclerosis, etc. Immunology is similarly making great strides but we need more information in order to treat the autoimmune diseases better and do away with the requirement after organ transplant for life-long immune suppression with drugs that have unfortunate side effects. In vaccines, academia-industry have contributed new vaccines that protect against hepatitis B (which causes liver cancer) and human papillomavirus (which causes cervical cancer), but we do not have enough information to succeed with a vaccine to protect against HIV infection, still a scourge on our society. While we have excellent treatments for a few cancers, the major cancers are still treated with chemotherapy with attendant side effects. Thus treatments for most breast, hormone-independent prostate cancer, colon cancer, lung cancer, brain cancer await new drugs which await new basic knowledge in order to identify targets. Other scientific disciplines are making important contributions that have the potential to open up new approaches to drug discovery.

A decade ago the human genome was deciphered. Over the last decade efforts were focused on determining the function of every gene in the human genome, and machines are becoming available to sequence the entire human genome for $1,000. Genomic information along with proteomic information and other "ome" information is pumping out tons of information that must be analyzed. That analysis has birthed a new discipline---computational biology, which attempts to put together all the information

pouring out of all the new machines to help identify new targets for drug discovery. Our near future will be based on full genome and proteome information and personalized medicine.

While we have an urgent need for new knowledge to attack the major diseases, NIH support for our researchers in academia is flagging. Perhaps the most worrisome thing for me is the observation of graduate students who are worried about getting funding in the future when they will apply for NIH research support---when they see their mentors struggling with constant writing of grants because so many are not adequately funded. With the current excitement in the biomedical sciences, our students should be looking forward to independent research and discovery rather than worrying about the first grant.

I obviously support increased support of NIH for the funding of fundamental research that will generate more information that will be the starting point for drug/vaccine discovery. Expenditures for the National Center for Advancing Translational Sciences (NCATS) by NIH might be incrementally helpful in the overall drug development continuum. For instance biomarker identification and validation would be helpful. Toxicology on a chip would also be interesting and might help. Training more clinical researchers is a good idea. But trying to find a use for a drug that has not been approved is a fishing expedition that has a very low probability of success. As for repurposing of drugs, I would recommend that the NIH not support clinical studies of marketed drugs. Such studies that are aimed at obtaining additional claims for drugs already being sold should be funded by the company that owns the drug and will benefit financially from the additional claim.

My advice to the Subcommittee: support the training of young scientists and then support their research so that they can try to fly on their own as soon as possible. We have seen revolutions in various areas of disease in the past, but there is much more that needs to be done. With the information accumulating in the biomedical sciences and talented young scientists coming along, we will see even greater accomplishments in the future---if we keep our eye on what is critical for drug discovery.