Testimony
*Of*

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Mr. Chairman, Ranking Member Jordan and Members of the Committee I am speaking from the perspective of a retired officer and practicing psychiatrist/researcher in the Public Health Service where I served in the Intramural Programs of the National Institutes of Health for 25 years and a just retired executive from the pharmaceutical industry. For the past 15 years I worked on discovering and developing drugs in two companies, Eli Lilly and Merck, which have had large investments in finding new drugs for brain diseases.

Despite the sensational advances in neuroscience during this period and explosion of sophisticated technologies within academia and industry we have not delivered truly novel drugs for diseases of the brain. All of the currently marketed major classes of drugs for brain disorders were discovered before the era of molecular science. While the current drugs for treating severe mental illnesses such as schizophrenia and depression are indispensable -- it would be difficult if not impossible to effectively treat these conditions without them -- they are unfortunately not as effective as we would desire. Fully 2/3 of patients with depression or schizophrenia never achieve full remission and another 1/3 do not respond much at all. Arguably the current generation of psychiatric medicines for treating schizophrenia, depression and severe anxiety are no more effective then the first generation of medicines discovered over 50 years ago -- and most of these by accident!

The assumption at all levels of government and industry that the scientific explosion beginning in the late 1980's would rapidly lead to more effective treatments was overly optimistic. If anything, the opposite has been the case. It now takes longer and costs several times more to deliver truly innovative drugs to the market than two decades ago as the bar has been raised.

Taking into account drugs for all diseases, only a half dozen first in class molecules are delivered per year at four times the cost. To bring a single new entity to market now costs, on average, of 1.8 billion dollars, a conservative estimate. The detailed assumptions and figures have been recently presented in a major journal with no one questioning their validity.[1] New drugs for brain diseases emerge at a much lower rate, prove more expensive to develop and carry one of the highest risks of any class in terms of negotiating the minefield of discovery and development.

What went wrong? It was assumed that understanding brain biochemistry and processes through modern science would increase the rate of matching specific abnormalities to specific drugs. After all, even with the science of the 60's, scientists had figured out that one could help Parkinsonism by replacing the

neurotransmitter dopamine. Coupling modern techniques with genetics. It seemed a sure bet to find many more such relationships between specific defects and diseases.

As my distinguished academic colleagues have or will testify in detail, most brain diseases have turned out to be much more complicated than anticipated. This is true both at the level of genetics and physiological processes. Instead of a few possible drug targets based on the model of one defect, one disease, we now consider hundreds without any established map or navigational tool. Animal models for brain diseases (with the exception of symptomatic epilepsy) have poor predictive qualities for human brain diseases. This is not surprising given species differences. Moreover, animals do not spontaneously show analogous conditions for such disorders as schizophrenia.

Investigators in the public and private sectors are therefore up against the wall of what we call "target validation"– put in other words, a valid target is one through which a specific drug produces benefit. Literally hundreds of potential therapeutic drug targets have been identified for our major psychiatric and neurologic diseases but only a handful of them validated. Almost all of the hundreds of targets identified through modern molecular science still require substantial resources and time to validate. Even without counting the years of basic science to suggest that a drug target is worth trying to validate in the clinic it requires an average of 13.5 years (2007 data) to discover and develop a compound and take it through regulatory review.[1] Moreover, only 1of 20 of central nervous system (CNS) drug targets selected for development will prove effective for some condition and reach the market.

There is no way, therefore, that the pharmaceutical industry can profitably deliver innovative and breakthrough medications for brain diseases to society without a paradigm shift. Levels of investment and time become even more prohibitive for developing drugs that might prevent or slow the progression of diseases, the Holy Grail of patients and clinical neuroscience. Given long development times and current laws many if not most drugs will have only 10 years or less of patent protection in the U.S. This is because in the U.S. the patent clock begins ticking when a patent is filed -- many years before the new medicine makes it to the market and importantly to the patient. . Since "me too" drugs are easier and more quickly developed, they enjoy longer patent protection

[1] Paul SM, Mytelka DS, Dunwiddle CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews Drug Discovery 2010 Mar 9 (3): 203-214

and have been a great economic driver. But they do not provide what patients are waiting for. Sadly, the period of patent exclusivity is not long enough to recoup the enormous R&D costs of the truly novel CNS drugs which are what we most want to pursue.

This is why many companies have reduced their investment in novel drugs for brain diseases, especially the major psychiatric ones such as schizophrenia and manic-depressive illness. Even those which remain heavily invested realize that they are unlikely to realize any profit from their most innovative drugs in the near term.

But for certain areas, such as Alzheimer's and other degenerative neurologic brain diseases, there is a willingness to take on such a risk because the need is so great. Senior leaders are over the age of 50 and know that without progress in slowing or preventing, for instance, Alzheimer's they stand a 50/50 chance of significant dementia by the time they are 90. Given society's success in treating heart disease and improving success with cancers, maintaining one's health until 90 is within reach for more and more of us but of dubious value if we are demented.

Many have now rallied behind this cause. The NIH, clinical scientists, patient advocacy groups, philanthropies, FDA and industry joined together under the umbrella of a remarkable effort led by the National Institute on Aging. It is called the Alzheimer's Disease Neuroimaging Initiative (ADNI) which, put simply is a collaborative effort to find so-called biomarkers of disease state, progression and drug response.[2] All findings go into the public domain as soon as the data is gathered and processed. This allows for the rapid standardization, quality control and sharing of methods to answer critical questions about patients and treatments as quickly as possible. The ADNI model has taken hold world wide. Currently the European Union, Japan, Australia and Korea have made support to such translational medicine initiatives for neurodegenerative disorders part of their national priority. The US based Alzheimer's Association, a patient advocacy group, has played a catalytic role in coordinating international efforts.[3]

We use the term "translational medicine" to cover all of the science and technology development activities required to take potential drug targets emerging from basic science and validate them as beneficial for human diseases.

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[2] Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack C, Jagust W, Trojanowski JQ, Toga AW, Beckett L. The Alzheimer's Disease Neuroimaging Initiative. Neuroimaging Clin N Am. 2005; 15(4):869-77, 2005.

[3] Carrillo MC, Sanders CA, Katz RG. Maximizing the Alzheimer's Disease Neuroimaging Initiative II. Alzheimer's Dement 2009; 5:271–5.

And it is an enhanced focus on translational medicine which offers the best hope for more effective application of basic neuroscience to brain diseases.

Public support of basic science through the NIH and other mechanisms has and continues to produce amazing advances. A robust private sector coupled with sophisticated regulatory oversight has delivered a wide range of safe drugs that increase longevity and quality of life. The introduction and use of an earlier generation of new drugs is estimated to account for 40% of the 2 year increase in average US life expectancy between 1986 and 2000.[4] But to realize the promise of more recent scientific advances we must invest much more in the tools of translational medicine, an area which has received much less focus support than basic science at one end or large clinical trials at the other.

The right balance of resources across the domains of basic research, translational medicine and clinical trials has yet to be achieved. And to do this most effectively, we need to expand the "open source" clinical data model pioneered by ADNI. Academic and government scientists, clinicians, drug developers, patients, industry representatives and legislators can work together to create a new paradigm of drug development that recognizes the current state of neuroscience as well as the interdependence across constituencies. We should not expect the paradigms established during the 60's and 70's to be optimal for establishing incentives and processes appropriate to modern neuroscience in the age of the Internet.

1. There are two specific, feasible and implementable initiatives that would pay high dividends in the shortest time. These can deliver because there is already a back-log of to-be-validated targets for brain diseases as well as many pockets of relevant data that are not generally available.
2. Open sharing of all relevant clinical data on characterization of disease state and drug response following proper anonymization to protect individual privacy

Putting the research tools and compounds held by both commercial entities and universities in the public domain ("pre-competitive space") as quickly as possible facilitated by innovative approaches to the Intellectual Property issues

Both of these initiatives require a degree of sharing and working together that is only possible in the age of the Internet and build on models which are already operable in several areas of science and society. When the public/private partnership around biomarkers for Alzheimer's was launched in 2004 many were

[4] Lichtenberg FR. The impact of new drug launches on longevity: evidence from the longitudinal, disease-level data from 52 countries, 1982-2001. Int. J. Health Care Finance Econ. 2005; 5: 47-53.

skeptical about the effects of putting clinical research data in the public domain as it was generated. What was then viewed as a risk is now appreciated as a important means of extracting the most information in the shortest time. Furthermore, one opens up the opportunity for a range of analytic approaches that go beyond anything that a single group of investigators could undertake.

The second initiative has been partly pioneered through entities such as the Foundation of the National Institutes of Health (FNIH) where government and industry can interact in a collaborative and "precompetitive" manner.[5] An important focus of the FNIH since 2007 has been to develop biomarkers, the research tools for translational medicine (The Biomarkers Consortium). There are other programmatic examples whereby companies have made compounds available to NIH for exploratory studies in schizophrenia, depression, alcoholism and drug abuse. On the other hand, the degree of academic, industry and government involvement is still tiny compared to the need. Stakeholders from all sectors are in discussions to see how more critical biomarker development can be put in the public domain.[6]

Multiple issues emerge when one brings together philanthropic, scientific , regulatory and commercial entities to invest in a common effort. None of these, however, are show stoppers.[7] Concerns include the potential conflict of interest of academic investigators and institutions as well as the traditional proprietary viewpoints of some. Some might ask, "Why should I pay for something that might benefit the business of other?" This, however, is no longer such a universally shared question from industry. As industry executives tackle the question of how to increase productivity, many recognize that there might be an advantage to having more aspects of drug development in the public domain ("pre competitive space") and operate companies in more of an open network fashion. But, for many, tools and methods are still viewed as intellectual property and know how which should be proprietary so as to protect one from the competition. Thus, the type of sharing involved in the Biomarker's Consortium of the FNIH can be a hard sell and dismissed as foolhardy from a business point of view. Given the expectation that businesses are profitable and deliver to shareholders, these leaders are not wrong to raise questions about sharing tools and methods that might help a competitor better develop its patented compound.

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[5] FNIH (Foundation for the National Institutes of Health). 2008. *FNIH.* http://www.fnih.org.

[6] IOM (Institute of Medicine). 2008. *Neuroscience biomarkers and biosignatures: Converging technologies, emerging partnerships.* Washington, DC: The National Academies Press.

[7] [7]IOM. 2009. *Venture philanthropy strategies to support translational research.* Washington, DC: The National Academies Press.

Might it be possible to create a set of laws and incentives that would facilitate sharing of the tools so that the real business would be to find the safest and most effective compound for a particular target? So, instead of having industry focusing on whether it can use internal know how to beat someone to the finish line with some particular version of what is essentially the same drug being pursued by several companies, it would compete around who actually has the best compound for an disease. The tools and methods for establishing the characteristics of a drug would be shared by all.

Furthermore, no single entity is large enough to develop and implement all of the sophisticated methods available to explore brain disease and drug treatment. Because any single institution can only focus on selected bits of the millions of data elements generated by modern studies, sharing data will increase the likelihood that important findings well be extracted. It is also possible that by such open sharing one might more readily figure out whether one's patent protected compound does or does not have commercial value. Industry might ultimately benefit more by sharing early clinical data than by trying to work within the silo of a single entity. What is needed is a nuanced set of laws and regulations that provide an incentive for the type of sharing that is certain to advance the field.

In conclusion, we now recognize that the implicit contract between publically funded research, government regulation and private drug development crafted decades ago does not deliver in the era of modern neuroscience. A paradigm shift toward much broader and earlier sharing of clinical data would have an immediate positive impact. A parallel broad collaborative investment in the tools of translational medicine would fill a gap and greatly accelerate the identification of valid drug targets. Innovative approaches to managing intellectual property concerns as well as periods of patent exclusivity should be given serious consideration to facilitate this transition.