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Introduction[1]

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD), are becoming increasingly prevalent in the United States due to an aging population (see, e.g., Alzheimer's Association, 2012; de Lau and Breteler, 2006; Hebert et al., 2003; Reitz et al., 2011; WHO, 2012).[2] Implications are grave for quality of life and health care costs (see, e.g., Alzheimer's Association, 2012; PDF, 2012).

Research on neurodegenerative diseases has expanded greatly over the past four decades (for example, see Young [2009]). Nevertheless, fundamental questions remain about the biology of these diseases, and further insights into the mechanisms of these diseases would help to inform the development of effective means to prevent and to efficiently treat them.

Traditionally, research and development efforts for neurodegenerative diseases have primarily considered individual diseases separately, and largely separate research communities and patient advocacy groups have emerged. Recent findings, however, have revealed certain commonalities in genetic and cellular mechanisms across neurodegenerative diseases. These findings suggest that it might be valuable—at least in some cases—to change the traditional way of studying these diseases by no longer seeing each as an independent entity, but rather as clinical variants of common cellular and molecular biological defects. This approach could help enhance basic scientific understanding of neurodegenerative disease, and could help with the development of biomarkers and new therapeutics.

In the spring of 2012, the Institute of Medicine's (IOM's) Forum on Neuroscience and Nervous System Disorders hosted a workshop to explore commonalities across neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, ALS, and FTD, and to identify potential opportunities for collaboration across the respective research and development communities. Participants came from academia; pharmaceutical and biotechnology industries; government agencies such as the National Institutes of Health and the U.S. Department of Veterans Affairs (VA); patient advocacy groups; and private foundations. Looking across the neurodegenerative diseases, workshop presentations and discussions aimed to do the following:

- Identify and discuss commonalities related to genetic and cellular mechanisms;

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[1] The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Institute of Medicine and they should not be construed as reflecting any group consensus.

[2] Overviews of neurodegenerative diseases and other neurological disorders, as well as lists of relevant organizations and other resources, can be found on the website of the National Institute of Neurological Disorders and Stroke: http://www.ninds.nih.gov/disorders/disorder_index.htm.

- Identify areas of fundamental science needed to facilitate therapeutics development; and
- Explore areas of potential collaboration among the respective research communities and sponsors.

CHARGE TO WORKSHOP PARTICIPANTS

In her opening remarks, Story Landis, director of the National Institute of Neurological Disorders and Stroke and cochair of the workshop planning committee, remarked that people who work on Alzheimer's disease and ALS, for example, typically have their own meetings and have few opportunities to "sit down, roll up their sleeves, and begin to talk about common mechanisms." This type of conversation, she said, could be extremely interesting and informative for participants working on these different diseases and could help advance understanding of potentially promising therapies. John Trojanowski, codirector of the Center for Neurodegenerative Disease Research at the University of Pennsylvania and cochair of the workshop planning committee, emphasized that the workshop format of shorter talks and extensive discussion periods was designed to encourage in-depth discussion among researchers specializing in different neurodegenerative diseases about the fundamental science and how this can drive therapeutic development.

Joel Kupersmith, chief research and development officer at the VA, which contributed funding for the workshop, charged workshop participants with identifying and discussing current research on commonalities across neurodegenerative diseases, research needs and opportunities, areas for collaboration among investigators and facilities, and infrastructure needed to advance research in this area. Kupersmith emphasized that the neurodegenerative diseases are a substantial part of the VA's research portfolio because the VA serves mostly an aging population. He also highlighted the potential for collaboration with VA investigators, who receive funding through the VA intramural research program.

ORGANIZATION OF THE WORKSHOP AND THIS SUMMARY

The workshop began with an examination of the rationale for examining commonalities across neurodegenerative diseases. Chapter 2 summarizes these presentations and discussions. Subsequent workshop presentations and discussions were organized around four topics: (1) protein aggregation and cellular mechanisms to prevent or eliminate it; (2) neurodegenerative disease transmission and immune therapy; (3) mitochondrial pathology in neurodegenerative disease; and (4) errors in RNA processing. These topics are summarized in Chapters 3 through 6, respectively. Given the time limits inherent in a 2-day workshop, it was not possible to exhaustively examine all possible cellular or genetic commonalities across neurodegenerative diseases. Planning committee members selected these four topics—from among various potential candidates—for discussion because of scientific interest in further exploring the mechanisms underlying these commonalities and/or the existence of promising therapeutics based on these mechanisms. Certain topics are well known to be shared mechanisms across many neurodegenerative diseases (e.g., protein aggregation), while others are in earlier stages of exploration (e.g., errors in RNA). Each chapter includes individual suggestions for future research priorities and other opportunities proposed by presenters during the workshop. The

statement of task is in Appendix B, the workshop agenda is in Appendix C and a list of registered participants is in Appendix D.

TOPICS HIGHLIGHTED DURING PRESENTATIONS AND DISCUSSIONS[3]

Several topics recurred across the 2 days of presentations and discussions. They are briefly summarized here, and discussed in much greater detail in subsequent chapters.

- **The need for a deeper understanding of cellular and molecular mechanisms, including those that may be common across neurodegenerative diseases:** The workshop was organized around exploring four mechanisms and pathophysiologies that appear to be common across multiple neurodegenerative diseases: (1) protein aggregation, (2) transmissibility, (3) mitochondrial pathology, and (4) errors in RNA. Some of these are better understood than others. For example, protein aggregation is a well-known commonality across many neurodegenerative diseases; mitochondrial dysfunction has been found across neurodegenerative diseases, although it is not known if it plays a causal role; and errors in RNA are at a much earlier stage of exploration. Regardless of how much attention a topic had previously received, there was a great deal of interest among many workshop participants in continuing to develop a deeper mechanistic understanding of the cell biology, both within a single disease and across diseases. Many participants suggested research questions about these mechanisms; examples are listed at the ends of the relevant chapters. Some participants noted the possibility of gaining a greater scientific understanding of these diseases through the examination of these commonalities; for example, perhaps understanding these commonalities better could shine light on why certain pathologies are found in multiple diseases with different clinical presentations.
- **Exploring commonalities across diseases may provide a promising approach:** Workshop presentations and discussions highlighted many reasons to pursue an approach of examining commonalities across neurodegenerative diseases. Participants discussed genetic and pathological overlaps across multiple neurodegenerative diseases, as well as genetic and cellular mechanisms that appear to be common across diseases, suggesting that cross-disease study could be appropriate and could help advance scientific understanding. A number of participants discussed various ways in which a cross-disease approach might help to advance therapeutics development, such as by leveraging findings from a disease that is better understood or easier to study to increase development of therapies for diseases that are less understood or harder to study. Participants also suggested a variety of pragmatic reasons to pursue this type of approach, such as sharing data and resources; combining areas of scientific and technical expertise; and tackling common challenges and barriers together.
- **A note of caution, however:** Several participants also emphasized, however, the importance of avoiding an "all or nothing" approach. They noted that it will be important to carefully examine the evidence and "tease out" when it makes sense to

[3] Rapporteurs' summary based on the presentations and discussions during the meeting and session chairs' summaries during the final session.

do cross-disease research and development and when the focus should remain on individual diseases. One participant raised the possibility that the diseases may have distinct initiating factors, but engage some common pathways at some point(s). There are also several examples in which promising approaches in one disease did not show similar promise for another disease, suggesting independent pathways in certain cases.

- **Therapeutic approaches based on common mechanisms:** Workshop discussions revealed significant interest in exploring ways to use the fundamental scientific understanding of these common mechanisms to drive therapeutic development. Presentations and discussions included some therapeutic approaches that are already at various stages of development, as well as ideas for promising new directions. Participants suggested various ways in which a cross-disease approach could help advance the development of therapeutics for neurodegenerative diseases. For example, one participant noted that identifying common threads across neurodegenerative diseases could help with target validation by at least showing that the result is based on multiple models rather than just one. Several participants noted that it might be helpful to start by testing new drugs in diseases that have features that make them easier to study (e.g., known genetic risk and onset estimate in Huntington's disease, shorter duration in Creutzfeldt-Jakob disease) before investing significantly in diseases that are harder to study (e.g., sporadic cases of Alzheimer's and Parkinson's diseases). Cross-disease therapeutic approaches could also enable cost sharing among disease-specific foundations and other entities, and could help reduce program risk by spreading it across multiple partners. One participant noted that a multiple-disease approach could be particularly beneficial for encouraging the development of therapeutics for rare diseases, if such a therapeutic also might be effective for a more common disease with a larger potential market.
- **Common challenges:** Participants discussed many challenges that are common across neurodegenerative disease research and development communities, and, in some cases, common to central nervous system (CNS) research and development in general. Examples included the lack of biomarkers, patient heterogeneity, lack of complete knowledge about the causes of these diseases, and the long latency before symptoms appear. Other challenges derived from problems with modeling neurodegenerative disease and impaired cognition in animals; and reliance on data from cell-free systems, cell cultures (often cells lines), and animal models, but rarely from human autopsy material.[4]
- **Opportunities:** Many participants highlighted opportunities to enhance the mechanistic understanding of these processes and diseases, and more generally to advance research and development. Some of these are specific to advancing research based on commonalities across neurodegenerative diseases. Others are topics

[4] Challenges and opportunities related to the use of animal models in research and development for nervous system diseases were explored in greater depth in a March 2012 workshop also hosted by the IOM Forum on Neuroscience and Nervous System Disorders. Titled *Improving the Utility and Translation of Animal Models for Nervous System Disorders,* a summary of the workshop is available online: http://www.nap.edu/catalog.php?record_id=13530 (IOM, 2013).

frequently raised in the context of therapeutics development for CNS disorders. Example opportunities and strategies included

- **Harmonizing measures:** Harmonizing genetic and pathology measures and developing pathological and clinical standards across diseases would provide a basis for further collaboration and research across neurodegenerative diseases, noted one participant.
- **Identifying and validating biomarkers:** Throughout the sessions, many participants commented on the need to identify and validate both diagnostic and therapeutic biomarkers. Many presenters discussed the current state of the art in biomarkers being used in their research, and also discussed critical gaps and needs; these comments are summarized in Chapter 2 and included in subsequent chapters as applicable.
- **Sharing resources, tools, and data:** In a variety of contexts, participants discussed the value of sharing resources, tools, and data among multiple investigators and/or academic and pharmaceutical entities. Examples of resources, tools, and data that could be shared included human genetics data to examine gene variants that may extend across disease populations, biomarker programs, iPS cells, compound libraries, enzyme-linked immunosorbent assays (ELISA), access to tissues, and access to analytic methods. Participants gave various examples in which pharmaceutical companies had already shared resources with academic investigators.
- **Collaborations and public–private partnerships:** Participants discussed a variety of potential collaborations and public–private partnerships that could help address some of the common challenges listed above. Several participants highlighted the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Parkinson's Progression Markers Initiative (PPMI)—large public–private consortiums that aim to validate biomarkers for their respective diseases—and suggested expanding this type of model to other diseases and arenas of investigation. Several participants also discussed the importance of collaborations between basic scientists and clinical researchers, and between academia and the pharmaceutical industry.
- **Funding:** Several participants suggested various funding mechanisms that could help support work that examines and leverages commonalities across diseases. Ideas included the development of dedicated programs and funding to identify commonalities; support specifically aimed at identifying targets and therapies that may benefit more than one disease; and support for collaborations among scientists interested in advancing this type of approach.