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A path toward understanding neurodegeneration:

A focus on cell biology may accelerate progress in disease prevention and cures

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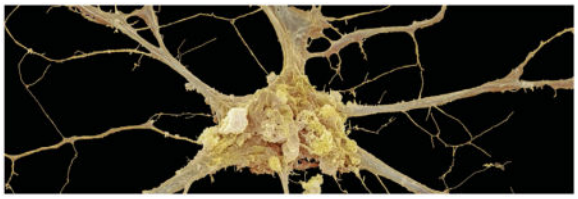
Graphical abstract

Understanding the fundamental basis of neurodegeneration requires a focus on cell biology (colored scanning electron micrograph of a neuron is shown).



The specter of neurodegenerative disease, particularly Alzheimer's disease, haunts the developed world and exacts a poorly documented toll on under-developed countries. With so little progress made toward finding a cure—or, better, a prevention—it is time to rethink the path to progress. This requires a change in perspective on the type of research that will make a difference. The lesson learned from cancer research is that a new commitment means rethinking the fundamental approach to the disease. Cancer research moved from taking potshots with, usually, cytotoxic drugs to a bottom-up, mechanism-based approach in which newly acquired genetic knowledge played the largest role. Today, that effort has produced a platform of knowledge from which academia and industry are drawing. For

SUPPLEMENTARY MATERIALS

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neurodegenerative disease, the genetic approach remains valid but the problem must concurrently be approached from a complementary, robust cell biological perspective, focusing on the cellular cascade of events that lead to neuronal cell death.

BUILDING ON INSIGHTS

If cell biology is the core discipline from which progress in neurodegeneration will emerge, then the research path forward needs to build on insights over the past two decades that have converged upon core cellular dysfunctions related to the disease. These include controls over protein folding, trafficking, and degradation; specific cell-type vulnerabilities; activation of aberrant signaling pathways that lead to cell death; and the interface of genomics and brain imaging with cellular-level resolution. For example, relevant cellular work is emerging from biophysical methods with high spatial and temporal resolution in vivo (1). This has revealed protein conformations with a liquid-liquid phase separation into protein-rich droplets that potentially link RNA granules and pathological inclusions (2). New information will emerge from identifying cell type–specific proteostasis networks that involve the unfolded protein response, the ubiquitin-proteasome system, and autophagy (3). Among several incipient clues are mutations that inactivate the ubiquitination and destruction of faulty or damaged mitochondria. Inhibiting this removal (by “mitophagy”) results in Parkinson’s disease (4). These early leads position the field of neurodegenerative disease squarely upon a deeper cellular basis and support investigative cell biology as a worthy strategy for formulating translational end points and rapid progress. Answers to why cells die (leading to neurodegeneration) will be as revealing as discoveries in the cancer field that explain why cells proliferate.

In the cancer field, critical insights emerged not from taking a shortcut toward therapy, but from a deep knowledge of genes and cells. In the field of neurodegeneration, there are unfortunate repeats of some of the same mistakes made earlier in the cancer field. In the United States, funding to acquire basic knowledge should not be siphoned off to support expensive, and at times risky, clinical trials based on inadequate knowledge. The shift from basic to applied research in the field of neurodegeneration was apparent at the U.S. National Institute of Neurological Disorders and Stroke (NINDS) (5), where, from 1997 to 2012, basic research funding by the agency declined from 87 to 71%, with support for the most basic research falling from 52 to 27% of the competing budget.

The impetus for presenting this proposal for cell biology as the foundational science for understanding neurodegeneration arose from a series of five salons held at sites around the United States in 2015 (see supplementary materials). The goal was to take a fresh and objective measure of neurodegeneration research from an informed group of scientists outside the field. To achieve this goal, the selected participants were deeply knowledgeable of the basic science topics faced by the neurodegeneration field, but for the most part had not been immersed in the field. This setting created lively discussions about the multifaceted nature of neurodegeneration, but held to the common theme of how a sustained basic cell science effort could lead to progress in the field.

THE FUNDING PATH

The need for a larger research effort on neurodegenerative disease is evident from the aging of the population and consequent epidemic prevalence of Alzheimer's disease. Hopefully, the next few years will see a large influx of dedicated funds from government and private sources in the United States. Indeed, the Bypass Budget Proposal for Fiscal Year 2017 (6) for Alzheimer's disease suggests this. What is also needed is clear guidance as to how funds can be spent with a substantial likelihood of success. When cancer research matured to the point that it could absorb funding in a productive way, and the U.S. "War on Cancer" was declared (1971), much of the money was well spent. However, considerable funds supported trendy work, such as the fruitless search for virus-induced human cancer. Savvy gatekeepers are needed who can funnel funds in promising directions. Here, however, lie challenges. Peer review is the long-standing decision-making mechanism for evaluating science, but when any field is dominated by a few long-held ideas and strong personalities, such a process may not be the best approach. Thus, attracting basic cell biologists to the study of neuro-degenerative disease will bring fresh ideas and insights. Also, collaborative large-scale efforts that require seeding by philanthropic donors, who are often less risk averse than government agencies, must operate in the context of advisers with open minds.

Funding comes with the question of establishing large-scale programs versus individual investigator-initiated grants. This debate is not an either-or matter, and there are intermediate blends of these tactics. What is important overall is to avoid setting unrealistic goals and timetables, which works against developing evidence for unobvious hypotheses. The many unknowns that neurodegeneration research faces make precise timetables unrealistic—another lesson learned from the effort put toward cancer research. The most remarkable discoveries come with a sense of surprise. The success of curiosity-driven science is a testimony to this path. A recent example is the development of gene editing tools such as clustered regularly interspaced short palindromic repeats (CRISPR) from a unique form of adaptive immunity in bacteria.

A CELL SCIENCE ENTERPRISE

Hand-in-hand with a defined scientific mission, the organization of a research enterprise with a cell science focus is critical to its success. An effective structure of a research entity that targets neurodegeneration will share many elements with other large biomedical entities. "Centers without walls" through the U.S. National Institutes of Health (NIH) represents a reasonable model for creating research entities. Its widely applicable core principles of cooperation, collaboration, and collegiality need to be balanced by the recognition of, and reward for, individual contributions and the freedom to engage in lively debate. The scientific effort should be inclusive of women and minorities, and without regard for national barriers. In the United States, streamlining grant support for investigators in their thirties could buck the longstanding statistic that first-time recipients of NIH RO1 grants tend to be over 40 years old. Sadly, Kaplan-Meier retention curves reveal that many principal investigators stop receiving NIH funding after they receive their first year of R01 funding (7). Such a discouraging funding environment drives students and young scientists away from a field. Instead, the opportunity for groundbreaking discoveries in the cell

biology of neurodegeneration should be a powerful global attractor for the next generation of scientists.

Cell biology requires a unique tool set, often centered around expensive microscopy, electrophysiological instrumentation, molecular probes, and image analysis. Therefore, research centers require dedicated watch-dogs that are alert to cutting-edge technologies and are responsive to engineering needs through in-house tool-building capacity. Robust communication and data-sharing technologies are also essential and become even more important in centers that operate beyond institutional boundaries. Technologies for video conferencing and user-friendly platforms for data sharing and retrieval will contribute to a productive center. Posting prepublication draft papers online through life-sciences preprint servers would accelerate deposition of research results into the public domain. Massive data collections such as the Alzheimer's Disease Neuroimaging Initiative (8) need to grow as a platform with broader applications and accessibility, while maintaining protection for patient privacy. As metadata analyses and semantic-level searches improve for diverse types of data, in silico research will increasingly contribute to gaining new insights. The vast existing literature in neurodegeneration, including reported findings that are no longer considered accurate, makes entry into the field challenging. Informetric sciences and meta-data extraction need development along with analyses of content that can capture research directions and knowledge gaps (9, 10). Such analyses may also reveal investigator networks that foster collaborations.

Economic and political shifts that have occurred since the "War on Cancer" have increased reliance of the research community on the private sector. Given the strong philanthropic history in the United States and the United Kingdom, philanthropists help shape the scientific trajectory of neurodegenerative disease research. Private partnerships with government and with academia are an effective strategy. Shared costs and greater freedom to operate in the private sector will allow a more nimble structure while avoiding the whimsical decisions that can tarnish donor-driven science. Private and academic institutions that have pioneered structures to accelerate discovery science in neurodegenerative disease include the Allen Institute for Cell Science, the Broad Institute, the Stowers Institute for Medical Research, the White-head Institute for Biomedical Research, and the Howard Hughes Medical Institute with its Janelia Research Campus. These institutes required enormous initial investments, but there are many structures through which smaller sums can make a difference. For example, the McDonnell-Pew Program in Cognitive Neuroscience is a lower-cost means to create an intellectual setting that attracts young scientists toward careers in neurodegeneration research. The Science Philanthropy Alliance helps philanthropists find a route to support basic scientific endeavors at any level.

A COMPREHENSIVE EFFORT

To sustain a basic science effort, the public must be engaged with evidence that well-executed discovery science is not only relwevant but necessary in the face of tempting promises of more short-term, high-risk treatments. Conquering neurodegenerative conditions requires a comprehensive effort that goes well beyond, but still begins with, basic cell science. A comprehensive effort cannot neglect improved clinical trial design, the economic

burden of care delivery, and the discovery of new pharmaceuticals. Each of these endeavors is contributory to the overall effort: a cure for, or mode of prevention of, neurodegeneration. Our message is that a redoubled effort toward understanding the fundamental basis of neurodegeneration will ultimately have the highest impact on solving this affliction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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