Crossroads: Two Points of View

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TARGETING THE LOW-HANGING FRUIT OF NEURODEGENERATION

Neurodegenerative diseases are the sixth leading cause of death in the United States,[1] but unlike other major causes of mortality, no significant disease-modifying therapies exist. Moreover, the number of patients with neurodegenerative disease is expected to nearly triple by 2050.[2] Without effective therapies, these disorders will devastate our health care systems, families, and millions of patients. The lack of treatments is not for lack of effort. In fiscal year 2011, the NIH spent $713 million on neurodegenerative disease research (http://report.nih.gov/index.aspx) and PubMed lists over 227,000 studies on neurodegeneration. So why are there no effective treatments?

While many challenges to drug development for neurodegenerative diseases have been suggested,[3–6] we suspect that a fundamental problem in trial design remains a critical factor. Trials have largely recruited patients by clinical features, including symptoms and neurologic examination findings. Although this allows maximum study generalizability by testing patients according to their neurodegeneration syndrome, it assumes that most participants share the same underlying disease mechanism or common pathway, or that the trial drug will influence disease progression despite a wide variety of disease mechanisms. These are risky propositions because patients can share a syndrome that results from common alterations in brain function but have drastically different underlying mechanisms of neurodegeneration. For example, loss of substantia nigra neurons leading to parkinsonism may result from (1) mutations in genes that regulate protein degradation (e.g., *PARK2*[7]), (2) mutations in genes controlling mitochondrial turnover (e.g., *PINK1*[8]), (3) mutations in genes with as yet unclear function (e.g., *LRRK2*[9]), (4) exposure to toxins, such as MPTP,[10] and (5) unknown causes (sporadic disease). Just as boosting PARK2 levels would not prevent Parkinson disease in those without *PARK2* mutations, an agent targeting only one pathway in a clinical trial may influence only a small subset of study participants. Because trials are powered with the assumption that all patients are potentially responsive, a drug affecting a subset of patients might be wrongly labeled as ineffective, killing future research. Such assumptions may delay the field for decades.

How can we select trial participants to maximize our chances of success? Recent trials have used CSF and neuroimaging biomarkers to study patients with specific neuropathologies. For example, many Aβ-neutralizing antibody studies are now only performed in patients with amyloid plaques.[11] Although this trial design represents an exciting advance, these studies assume that plaques identify patients whose disease is caused by Aβ. Alternatively, as evidenced by Aβ deposits in unimpaired elderly adults,[12] Aβ may be present but not mechanistically linked to disease in some patients. Trials that group patients by and target Aβ, tau, or other biomarkers risk failure if these proteins are coincident with—rather than causative of—disease.

As an alternative to enrolling patients using only clinical features or biomarkers, we propose studying patients with a known mechanistic trigger—patients with a gene mutation that causes a well-defined clinical syndrome. In the past decade, many highly penetrant mutations have been identified.[13,14] Many are rare compared to the total number of patients with a given neurodegenerative disease (table 1), but some are sufficiently prevalent to enroll patients on the basis of genotype (table 2).

A genetic approach to drug development and trial design has achieved impressive results for nonneurologic disorders. For example, ivacaftor is effective in a small subset of patients with cystic fibrosis (CF). Around 90% of patients with CF express little cell-surface CF transmembrane conductance regulator (*CFTR*); however, the CF-evoking mutation *CFTR* G551D results in a poorly conducting but correctly localized channel in 4% of patients. Ivacaftor enhances CFTR conductance and thus lung function in G551D patients.[15,16] Trastuzumab, a monoclonal antibody against HER2, is another genetically targeted therapy. Trastuzumab significantly extends life in patients with HER2-positive tumors.[17] Importantly, trastuzumab would not have shown efficacy in a clinical trial enrolling all patients with breast cancer as only 20% of breast cancer patients are HER2-positive.[18]

Developing and testing therapeutics based on mutation status is not without challenges. First, drug

Table 1 Most common causes of neurodegeneration grouped by clinical syndrome

	Clinical syndrome	Prevalence[a]	References
1	Alzheimer disease	1,240	21
2	Parkinson disease	320	22
3	Dementia with Lewy bodies	52	23
4	Frontotemporal dementia	14	24,25
5	Huntington disease	14	26
6	Myotonic dystrophy type 1	5.6	27
7	Amyotrophic lateral sclerosis	4.7	28
8	Spinocerebellar ataxias	3.0	29
9	Progressive supranuclear palsy	2.8	30
10	Gaucher disease	1.8[b]	31

[a] Prevalence in US/Western populations (per 100,000; all ages).
[b] Inadequate epidemiologic data are available; prevalence given is per 100,000 live births.

discovery is never straightforward, even in diseases with a known genetic target. Many causative genes in neurodegeneration are scaffolds, structural proteins, and other nonenzymes that are difficult to target directly. Even after a suitable target has been identified, extensive pharmacologic and chemical studies are required. However, several new technologies hold promise for genetic disease, including antisense oligonucleotides (ASO). For patients with known mutations, ASO bypass the challenging target identification process as they allow allele-specific knockdown of virtually any gene. With ASO, any gain-of-function neurodegenerative disease gene—and even some loss-of-function genes— is "druggable." In 2014, a phase III clinical trial will assess the use of ASO to treat spinal muscular atrophy (http://quest.mda.org/news/sma-isis-smnrx-shows-benefit-infants-children), a disorder caused by loss-of-function mutations in *SMN1*; in this case, the ASO rescue loss of SMN1 by promoting alternative splicing and therefore full activity of a conserved gene, *SMN2*. More trials, including one in Huntington disease, are expected in 2015.

After drug discovery, clinical trials for genetic forms of neurodegeneration will present more challenges. While most neurodegenerative disorders have a familial form caused by known gene mutations, these inherited variants constitute a small fraction of total cases (tables 1 and 2). It is thus costly and time-consuming to recruit patients by genotype. One strategy, which could partially mitigate this problem, is to incorporate substudies of patients with genetic disease into larger trials including mostly sporadic patients. Another innovative trial design, the adaptive I-SPY 2 trial design, which assigns breast cancer patients to multiple different treatment arms according to the mutations found in their tumors,[19] could be applied to neurodegeneration and may further improve trial outcomes. Another challenge is that studies or substudies of patients with genetic forms of neurodegeneration will necessarily be small; therefore, these studies will be powered to detect only relatively large effects. We do not see this as a disadvantage; the identification of therapies with large effects should be a priority in neurodegenerative disease research. Finally, the relatively modest financial reward for targeting uncommon genetic diseases may dissuade investment. However, many large biotechnology companies are increasing their focus on rare diseases, and some companies have successful drug portfolios solely targeting rare diseases. The potential efficacy

Table 2 Most common causes of neurodegeneration grouped by known genetic cause

	Mutated gene[a]	Associated clinical syndrome	Mode of inheritance	Prevalence[b]	References
1	*HTT*	Huntington disease	Autosomal dominant	14.0	26
2	*LRRK2*[c]	Parkinson disease	Autosomal dominant	13.7	32
3	*DMPK*	Myotonic dystrophy type 1	Autosomal dominant	5.6	27
4	*PSEN1*	Alzheimer disease	Autosomal dominant	3.0	33
5	*C9ORF72*	Amyotrophic lateral sclerosis, frontotemporal dementia	Autosomal dominant	1.9	34,35
6	*GBA*	Gaucher disease	Autosomal recessive	1.8[d]	31
7	*MAPT*	Frontotemporal dementia	Autosomal dominant	1.4	36
8	*FXN*	Friedreich ataxia	Autosomal recessive	1.3	37,38
9	*SMN1*	Spinal muscular atrophy	Autosomal recessive	1.2	39
10	*PGRN*	Frontotemporal dementia	Autosomal dominant	1.0	40–43

[a] Only major genes (those exhibiting autosomal dominant or recessive inheritance and causing neurodegeneration with 70%–100% penetrance) are included; other genes are omitted. The most common genetic risk factor for neurodegeneration is polymorphism in *APOE*. The number of patients with Alzheimer disease attributable to *APOE* ε4 homozygosity is 120 per 100,000.[44,45] Lifetime risk for Alzheimer disease in individuals with *APOE* ε4 homozygosity is 51%–60% (depending on sex) at age 85.[46]
[b] Prevalence in US/Western populations (per 100,000; all ages).
[c] Because *LRRK2* exhibits the lowest penetrance of the genes listed, the number of patients with Parkinson disease with a mutation in *LRRK2* is reported. Lifetime risk for Parkinson disease in individuals with *LRRK2* mutations is 74% at age 79 years.[47]
[d] Inadequate epidemiologic data are available; prevalence given is per 100,000 live births.

and profitability of targeting genetically at-risk populations have already encouraged biotechnology leaders to start grouping patients by genotype. For example, Genentech's upcoming trial of crenezumab will include 100 Colombian patients with mutations in *PSEN1* (http://www.clinicaltrials.gov/ct2/show/NCT01998841). Additionally, the Dominantly Inherited Alzheimer Network is recruiting patients with known genetic causes of Alzheimer disease to participate in trials and tissue banking. An important trial examining an anti-Aβ antibody (solanezumab) in patients with mutations leading to increased Aβ fragments (*APP* and *PSEN1* mutations) is underway (http://www.clinicaltrials.gov/show/NCT01760005). Both of these trials are enrolling very young patients who are either asymptomatic or mildly symptomatic; one advantage of studying patients with genetic disease is the ability to identify those who will develop neurodegeneration before symptoms appear, as early intervention may be crucial in halting the disease process.

Identifying a disease-modifying therapy—in any population regardless of size—is the most pressing issue in neurodegeneration research. Prior trials have prioritized study designs that would impact a large number of patients, but it may be time to retarget the lowest hanging fruit, no matter how modest the size. We do not advocate ceasing clinical trials in patients with sporadic forms of neurodegeneration—trials in genetic and sporadic disease are not mutually exclusive—but we do advocate devoting more resources and time to trials of patients with genetic disease. If the first effective treatment for neurodegeneration is identified in patients with genetic disease, it may prove efficacious in a broader population of patients who share the same underlying disease mechanism as the genetic patients. This has previously been seen with familial hypercholesterolemia and statin treatment.[20] A successful therapy will also catalyze renewed academic and industry investment in translational neurodegeneration research. Thus, we are optimistic that effective therapies for neurodegeneration can be identified through clinical trials designed with the best chance for success.

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NOURISH THE ROOTS WHILE PICKING THE FRUIT

Mason et al. present a cogent argument for orienting clinical trials for neurodegenerative syndromes toward genetic mechanism–defined disease subtypes. As they point out, disease-modifying clinical trials for neurodegenerative disorders have been largely disappointing. Mason et al. make the unimpeachable point that a likely source of failure is the implicit assumption that trial participants recruited on the basis of broadly defined clinical syndromic features share relevant common mechanisms of neurodegeneration. Heterogeneous trial populations will obscure detection of therapeutic effects in a mechanistically relevant subgroup.[1] Mason et al. propose taking advantage of

our burgeoning knowledge of the genetics of neurodegenerative disorders to focus on relatively pure subpopulations.

Some of the assumptions underlying this logical argument are partially incorrect, however. Mason et al. comment that we lack disease-modifying treatments for neurodegenerative syndromes. This may not be true for the most common clinical syndrome associated with neurodegeneration—dementia. Epidemiologic data suggest the existence of several modifiable risk factors for dementia, including diabetes, midlife hypertension, midlife obesity, depression, smoking, cognitive inactivity or low educational attainment, and physical inactivity.[2] Barnes and Yaffe[2] estimated that modest (10%–25%) reductions in all these risk factors could significantly blunt the anticipated rise in dementia prevalence likely in coming decades. Recent data support this prediction. Results of several large epidemiologic studies in the United States and Europe (reviewed concisely by Larson et al.[3]) suggest that age-related incidence and prevalence of dementia is falling and the magnitude of the reported changes is substantial. What could account for these encouraging findings? Two potential important interventions are better control of vascular risk factors and rising levels of education in the post–World War II decades. In large autopsy series, cognitively impaired individuals commonly exhibit mixed pathologies, very often a combination of vascular and neurodegenerative pathologies. In many cases, dementia is undoubtedly the result of cumulative effects of neurodegeneration and vascular brain injuries. There is preliminary evidence that similar phenomena occur in Parkinson disease.[4] The other suggested protective intervention, education, may protect against cognitive impairments by increasing cognitive reserve, raising the threshold for brain injury sufficient to cause symptomatic cognitive impairment. The effects of increasing education and control of vascular risk factors may overlap. Considerable evidence indicates that improved education, particularly early in life, is associated with better health behaviors, including diminished vascular risk factors.[5] We should not be complacent, but we may already be experiencing benefits of interventions that significantly mitigate the anticipated increasing incidence of dementia syndromes associated traditionally with age-related neurodegenerative pathologies. A limitation of the existing epidemiologic data is that they are primarily observational. Randomized clinical trials of interventions for modifiable risk factors for dementias are, however, unlikely to be feasible over the longer time frames required to demonstrate effects definitively. Instead, the accumulation of data from several observational studies is likely to form the best means of evaluating these interventions. Treatment of modifiable risk factors for dementia will certainly not eliminate all dementia but existing interventions should be extended aggressively while primary treatments for neurodegeneration are pursued.

Another problematic assumption made by Mason et al. is the notion that genetically defined forms of neurodegenerative disorders are "low-hanging fruit." The most common genetic neurodegeneration mentioned by Mason et al. is Huntington disease (HD). The research experience with this devastating disorder is a sobering reminder of the difficulties of developing genetic mechanism–based therapies. The expanded polyglutamine repeat mutation of the *huntingtin* (*HTT*) gene that causes HD was described over 20 years ago.[6] HD research attracted an impressive array of scientific talent and is pursued with the most powerful methods of modern biology. Most workers in the HD field will admit that developing effective therapies has proven more difficult than anticipated. One plausible explanation for our failure to develop useful treatments is that mutant *HTT* appears to have multiple pathogenic modes of action,[7] precluding the development of a magic bullet targeting a susceptible node in a well-defined pathogenic cascade. Similar phenomena may occur in other genetic neurodegenerative diseases such as spinocerebellar ataxia type 1 and frontotemporal dementia/motor neuron disease secondary to mutations in the *C9ORF72* gene.[8,9] We have to be realistic about the challenges of developing genetic mechanism–based therapies.

Mason et al. refer to experiences with genetically defined malignancies as positive examples of their preferred approach. These examples are unquestionably valid and the approach advocated by Mason et al. is conventional thinking in oncology. With the important exception of breast cancer, however, the greatest successes in oncology have little to do with genetic mechanism–defined treatments. The largest components of the decline in cancer deaths in the past few decades are prevention strategies: Pap smears, screening colonoscopy, and tobacco abuse reduction. These distinctly nonindividualized interventions are not only highly effective but relatively inexpensive.

The prescription of genetic mechanism based–trials is a rational and perhaps necessary way forward for developing treatments for neurodegeneration. It is likely, however, that a pluralistic approach to prevention strategies and treatments for neurodegenerative disorders will yield the best results. Mason et al. mention the large amount that NIH spends on neurodegeneration research. It should be recalled that much of this money is spent on precisely the type of mechanistic research needed to underpin the genetic-based trials advocated by Mason et al. My

experience is that NIH review panels are biased toward this type of research. We are a wealthy enough nation to pursue many avenues of research and treatment in this important area.

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