



Alzheimer Disease in 2020

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Remarkable advances in unraveling the biological underpinnings of Alzheimer disease (AD) have occurred during the last 25 years. Despite this, we have made only the smallest of dents in the development of truly disease-modifying treatments. What will change over the next 10 years? While the answer is not clear, we make several predictions on the state of the field in 2020, based on the rich knowledge described in the other contributions in this collection. As such, our predictions represent some of the principal unresolved questions that we believe deserve special investigative attention in the coming decade.

It is a challenge to prognosticate in any field of science, and this is certainly the case in the enormously complex area of Alzheimer disease (AD). Nonetheless, both laboratory and clinical research in this field have moved forward at a rapid pace. Based on what we know in 2011, we make some predictions for what the landscape will look like in 2020 and just beyond.

GENETICS

Great progress has been made in identifying and mechanistically characterizing genes that cause autosomal-dominant, early-onset AD: *APP*, *PS1*, and *PS2*. Moreover, *APOE4* has been found to be by far the strongest genetic risk factor for late-onset AD. Single nucleotide polymorphisms in several other genes have recently

been shown to be associated with increased or decreased risk for developing late-onset AD. Although their contributions to genetic risk are statistically significant in various populations, they have much smaller effect sizes than that of *APOE*. By 2020, with the advances in whole-genome and exome sequencing, a large percentage of all genes and DNA sequence variations contributing importantly to AD will probably have been identified. This will have occurred not just for genes that play a small role in overall risk, but also for genes that represent rare variants that actually cause AD. The genetic discoveries will increasingly be driven by the use of endophenotypes such as quantitative assessments of clinical variables, brain imaging, and cerebrospinal fluid (CSF) and plasma biomarkers, combined with advanced informatics methods. New genetic findings

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combined with molecular and systems biology approaches will have identified several signaling pathways contributing to AD for which targeted therapies will be in development.

PROTEIN AGGREGATION

It is increasingly clear that AD, like most other neurodegenerative diseases, is fundamentally a disorder of altered protein folding and aggregation. In the case of AD, the two primary culprits appear to be amyloid β -protein ($A\beta$) and tau. One of the difficulties in studying disorders of protein misfolding and misassembly relates to the tools available to study the proteins of interest. By 2020, it is likely that more sensitive and specific tools will be available to sense and detect monomers, oligomers, and fibrils of $A\beta$, tau, and other proteins that aggregate in neurodegenerative diseases. It is likely that we will be able to distinguish these different assembly forms not only in vitro but also in intact cells and in vivo, in both animals and humans. The correlations between the presence of various protein conformations and cellular, synaptic, and brain network dysfunction will be much clearer than they are now. By 2020, the ability to monitor such protein forms will have enabled several new compounds targeting $A\beta$, tau, apoE, or other molecules strongly implicated in AD pathogenesis to be developed and to enter prevention or treatment trials. Mounting data suggest that the spreading of diffusible oligomers and other protein aggregates from cell to cell within the brain, probably through specific neuronal networks, may contribute to AD progression. By 2020, we predict that it will be more clear whether a prion-like mechanism of spread, in particular for the tau protein, is an important pathogenic feature of AD, and therapies targeting this spread may have been shown to have benefits in animal models and be ready to enter human trials. It has become apparent that a complex network of cell biological pathways and processes regulates both normal and abnormal protein folding, the so-called proteostasis network. How aggregates of $A\beta$ and tau are related to this network and to autophagy, proteasome function, and cell signaling pathways

that influence proteostasis will be better understood and used to develop novel treatments.

CELL BIOLOGY OF NEURODEGENERATION

Although quite a lot is known about the cell biological underpinnings of AD, we may have only touched the tip of the iceberg. Although we do not expect things to be crystal clear by 2020, several advances are likely to have taken place. The sequence and time course of biochemical, cellular, and neurovascular abnormalities that contribute to brain dysfunction in AD should be better understood, including at which AD stages synaptic dysfunction, inflammation, and frank neuronal death contribute to various clinical features of cognitive impairment. Importantly, we will have a better understanding of the nature of brain dysfunction at different stages of AD-type pathology in both animal models and humans, owing to the advent of more sophisticated tools to study micro- and macrolevel brain circuitry and synaptic transmission. These tools are already emerging in the area of basic neurobiology, and the growing interplay between this field and the applied study of AD will be more intense than it is now. Importantly, by 2020, we will better understand $A\beta$ and tau metabolism in vivo and how different factors both inside and outside of the central nervous system contribute to levels of these molecules in different cellular and bodily compartments. The rate-limiting steps in the biosynthetic and clearance pathways that regulate the levels of these proteins and are thus attractive for therapeutic targeting will become more apparent. The detailed mechanisms of how apoE influences $A\beta$ aggregation and clearance as well as the molecules that mediate this process will be rapidly advancing. Whether and how apoE4 also contributes to AD via non- $A\beta$ -related mechanisms will become apparent, and apoE-based therapies will probably be entering clinical trials.

The issue of whether monomeric $A\beta$ has a robust and specific normal function will have been clarified, and whether and how APP metabolites other than $A\beta$ play a pathophysiological role in AD will have been better sorted out. The emerging linkage among brain energy

metabolism, neuronal activity, and the regional vulnerability to AD pathology will be much better understood. Lifestyle factors and possible pharmacological manipulations to influence them will become a more active area of research in both animals and humans. Beyond A β and tau, how factors related to aging, bioenergetic stress, brain injury/ischemia, and newly identified genes contribute to the progression of neurodegeneration will be under study at the organismal and cellular levels. Investigators will probe receptors, signaling pathways, and effectors that explain how A β accumulation leads gradually to tau alteration and the impaired function and structure of neuronal processes.

CELL-CELL INTERACTIONS AND INFLAMMATION

In several neurodegenerative diseases, there is now evidence of both cell-autonomous and non-cell-autonomous processes that contribute to pathogenesis. Considerable progress in this area should occur during the coming decade by studying genes recently implicated in AD, new stem cell technologies, novel approaches to neurogenesis, and improved rodent models of cell-autonomous and non-cell-autonomous processes, with attendant therapeutic implications. Integration of findings from cellular models with animal models to understand the impact of cellular changes on physiology and network function will provide new insights into what is important and what is not in AD pathogenesis in vivo. Importantly, integrating cellular studies with improved animal models that develop multiple features of AD without marked overexpression of AD genes will produce a better understanding of how A β accumulation is linked to downstream neurotoxicity, including, for example, how it leads in different individuals to exacerbation of principally tau or principally synuclein aggregation in tangle-rich AD versus the Lewy body variant of AD. This quest will be facilitated by novel methods that allow for quantitative assessment in animals and humans of synaptic function locally and in networks during the evolution of AD pathophysiology and following application

of agents targeting specific molecules/pathways. Whereas it is already clear that neuroinflammation is involved in AD pathogenesis, we will better understand by 2020 the roles of astrocytes, microglia, complement components, cytokines/chemokines, and the peripheral immune system in both contributing to neurodegeneration and protecting against it. Based on this information, both prevention and treatment trials with immunomodulatory drugs targeting specific pathways in the innate or adaptive immune systems will be in various stages of development.

CLINICAL TRIALS AND TREATMENT

At this writing, the only medications that have an impact, albeit modest and transient, on the cardinal symptoms of patients with mild to moderate AD dementia are acetylcholinesterase inhibitors and an NMDA receptor antagonist. It appears that the pathology of AD begins to develop 10–20 or more years prior to currently recognizable clinical signs of AD. By the time the clinical phenotype is recognized, substantial synaptic and neuronal degeneration and profound inflammatory changes have already occurred. For therapeutics to have a significant impact on delaying or actually preventing AD, it is likely that patients will need to be diagnosed at the stage of preclinical AD (i.e., presence of AD neuropathology but no clear clinical manifestations) or during early symptomatic AD, and then be given disease-modifying agents. By 2020, several trials of promising disease-modifying therapies will have been initiated and perhaps even completed through public–private consortiums in which asymptomatic subjects with early-onset familial AD or late-onset AD are identified via biomarkers as having a high risk to convert to the symptomatic stage over the following 3–5 years. All AD clinical trials, by the time they reach late phase 2, will use experimental treatments that have been shown by biomarker criteria to be hitting their intended target in man. It is very likely that one or more of these secondary prevention—or presymptomatic—trials will be in phase 3, and that phase 2 data will have strongly

Table 1. Alzheimerology in 2020

Risk assessment at around age 50 and then every 10 years:
History (emphasizing family history) and neurological exam
Brief cognitive screen and neuropsychological testing
Gene screen on “AD risk chip” (+ other familial dementias)
Imaging—A β scan, tau scan, MRI
Blood “A β antibody challenge”: basal and evoked A β levels
CSF assays for A β , tau, and other biomarkers
Outcome: a numerical AD risk score

suggested that not only have biomarker levels improved, but also a slowing of the subtle decline in memory and executive function has occurred. It is also likely that, by 2020, one or more new symptomatic agents for AD will have been approved by regulatory agencies for those with clinical AD, supplementing the symptomatic agents currently available. Therapies based on altering presymptomatic subjects’ behaviors such as diet, exercise, sleep, etc., will also be in the process of evaluation, to determine whether they prevent the onset of AD pathology in asymptomatic middle-aged people.

A much hoped-for outcome of the intensive therapeutic research reviewed by Schenk et al. (2011), Lee et al. (2011), and Aisen et al.

(2011) is that at least one of the agents currently in phase 2 or 3 clinical trials will have shown sufficient efficacy and safety to have been approved as the first disease-modifying treatment for AD. However, even if this central goal is only achieved after 2020, it has become apparent that a new diagnostic and therapeutic paradigm is entering the AD field. Some hypothetical features of this emerging clinical paradigm, which probably will not come to full fruition before 2020, are described in Tables 1 and 2. Such a management approach, elements of which are almost feasible today, indicate that AD is steadily moving toward the kind of combined diagnostic–therapeutic algorithm that patients with cardiovascular disease already benefit from.

SUMMARY

The completion of this multifaceted collection signifies the rich progress in unraveling the biology and clinical science of AD that has occurred during the last quarter-century. Yet the field has not achieved success in validating a disease-modifying drug based on an understanding of AD pathogenesis. We suspect that this situation will change soon and predict that, by 2020, the enormous scientific investment will have begun to pay off, and we will be on the verge of treatments that may delay the onset of AD in many millions worldwide.

Table 2. A new paradigm for managing AD based on the AD risk category into which a person falls

Risk category	Treatment
1. Presymptomatic subjects with no evidence of A β accumulation in the brain and high risk based on genetic, plasma, or CSF studies	1. A β synthesis or oligomer inhibitor 2. A β synthesis or oligomer inhibitor A β vaccination (active or passive)
2. Presymptomatic subjects with evidence of A β accumulation in the brain	3. A β synthesis or oligomer inhibitor + A β vaccination (active or passive)
3. Presymptomatic subjects with evidence of A β and tau/synuclein accumulation in the brain	Anti-tau/anti-synuclein therapy
4. Symptomatic subjects with evidence of A β and tau/synuclein accumulation in the brain	4. A β synthesis or oligomer inhibitor + A β vaccination (active or passive) Anti-tau/anti-synuclein therapy Neuroprotective agents Symptomatic agents, e.g., cholinesterase inhibitors, memantine, other neurotransmitter modulators, other psychotropic treatments

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*Reference is also in this collection.

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