

Translating the biology of aging into novel therapeutics for Alzheimer disease

Yuko Hara, PhD, Nicholas McKeenan, BS, and Howard M. Fillit, MD

Neurology® 2019;92:84-93. doi:10.1212/WNL.0000000000006745

Correspondence

Dr. Fillit

hfillit@alzdiscovery.org

Abstract

Aging is the leading risk factor for most chronic illnesses of old age, including Alzheimer disease (AD), a progressive neurodegenerative disease with currently no therapies that prevent, slow, or halt disease progression. Like other chronic diseases of old age, the progressive pathology of AD begins decades before the onset of symptoms. Many decades of research in biological gerontology have revealed common processes that are relevant to understanding why the aging brain is vulnerable to AD. In this review, we frame the development of novel therapeutics for AD in the context of biological gerontology. The many therapies currently in development based on biological gerontology principles provide promise for the development of a new generation of therapeutics to prevent and treat AD.

Introduction

Advances in medicine, public health, and education have resulted in increased human lifespan, and the elderly population has grown dramatically worldwide. The increase in lifespan, however, has been accompanied by an increase in age-related chronic diseases, including type 2 diabetes mellitus, cardiovascular disease, cancer, osteoporosis, and neurodegenerative diseases.¹ In fact, morbidity rates increase steadily to middle age, then increase at a much steeper rate such that it is twice as high in people over 80 compared to 60- to 64-year-olds, a phenomenon related to the Gompertz curve.²

Geroscience is a multidisciplinary field that examines the relationship between biological aging and age-related diseases.³ The trans-NIH Geroscience Interest Group Summit discussed 7 processes that contribute to biological aging: macromolecular damage, epigenetic changes, inflammation, adaptation to stress, and impairments in proteostasis, stem cell regeneration, and metabolism.¹ Intriguingly, these 7 processes are highly intertwined with one another. Thus, targeting the common biological processes of aging may be an effective approach to developing therapies to prevent or delay age-related diseases.

The leading risk factor for sporadic Alzheimer disease (AD) is also aging. Processes that are altered with aging that have been implicated in AD include inflammation, impaired autophagy, mitochondrial dysfunction, vascular problems, epigenetic changes, and synaptic loss (figure). An increased incorporation of extensive knowledge regarding biological gerontology into research on AD would likely increase our productivity in developing new drugs for AD.

From the Alzheimer's Drug Discovery Foundation, New York, NY.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article. The Article Processing Charge was funded by a donation to the Alzheimer's Drug Discovery Foundation by an anonymous foundation.

The Article Processing Charge was funded by a generous donation to the Alzheimer's Drug Discovery Foundation by an anonymous foundation.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Glossary

A β = β -amyloid; AD = Alzheimer disease; FDA = Food and Drug Administration; HDAC = histone deacetylase; IL = interleukin; TUDCA = tauroursodeoxycholic acid.

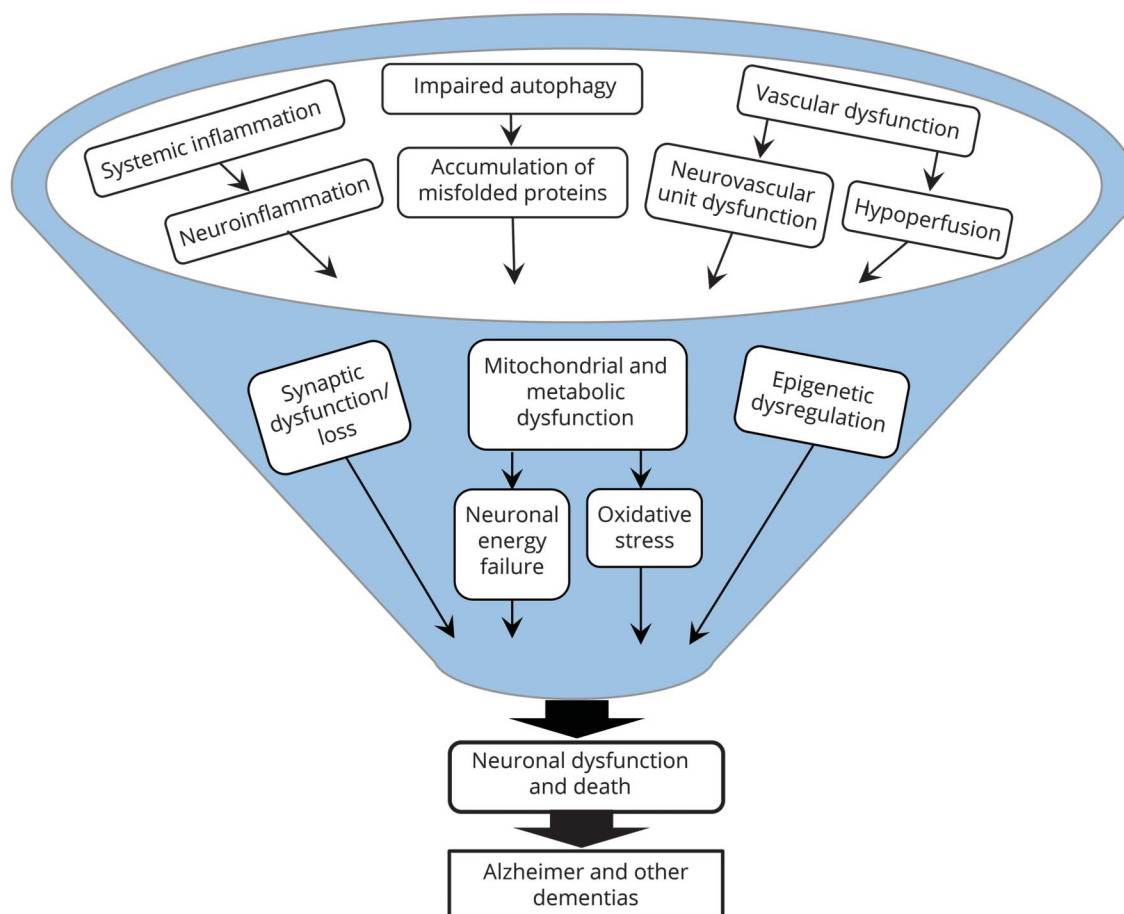
Pathologic hallmarks of AD

Pathologic hallmarks of AD include senile plaques comprising β -amyloid (A β) proteins along with many other misfolded proteins and neurofibrillary tangles formed by hyperphosphorylated tau protein aggregates. The accumulation of plaques and tangles occurs over many decades, in association with aging. While A β can be detected in early adulthood even in cognitively healthy people, elevated amyloidosis begins in the 6th decade of life and increases linearly into old age.⁴ Medial temporal tauopathy also begins in middle age and overt cognitive impairment coincides with increased neurofibrillary tangle burden.⁵ Clearly, pathologic and clinical findings indicate that sporadic AD and related dementias are age-related diseases.

Although A β plaques and neurofibrillary tangles are pathologic markers of AD, it is not known if these pathologies represent valid drug targets or if these targets alone are sufficient to treat AD. The current drug development pipeline strongly reflects focus on these 2 major pathologic proteins, with 32.5% of the currently ongoing 126 AD clinical trials targeting either A β (30/126, 23.8%) or tau (11/126, 8.7%). Of phase 3 trials, 52% (13/25) are pursuing these targets (12 targeting amyloid and 1 targeting tau).⁶ Therapeutic attempts to remove or decrease the production of A β have appeared promising in preclinical and early-phase trials, but have been largely unsuccessful in altering the progression of AD in later-phase clinical trials.⁷

Because the mechanisms underlying AD and related dementias are complex and multifactorial, greater

Figure Age-related changes in biological processes contribute to neurodegeneration in Alzheimer disease (AD) and other dementias



Processes that are altered with aging that precede neurodegeneration include inflammation, impaired autophagy, vascular dysfunction, synaptic loss, mitochondrial and metabolic dysfunctions, and epigenetic changes. These processes provide numerous novel targets for new drug development for AD.

exploration of targets beyond these 2 pathologic markers is warranted.

Inflammation

Inflammation is a hallmark of aging. Inflammaging refers to the low-grade, chronic, systemic inflammation associated with aging in the absence of overt infection and is a significant risk factor for morbidity and mortality in the elderly.⁸ Furthermore, in middle-aged and older adults, higher levels of systemic inflammatory markers (e.g., C-reactive protein, interleukin [IL]-6, fibrinogen) are associated with cortical thinning,⁹ lower and greater declines in regional cerebral blood flow,¹⁰ and poorer cognitive functions, including executive function and learning and memory.¹¹ However, randomized clinical trials of broad-spectrum anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (e.g., naproxen, aspirin, celecoxib) and others (e.g., prednisone, statins, rosiglitazone) have thus far failed to improve cognitive outcomes in patients with AD.¹² Currently, there are 12 ongoing clinical trials testing anti-inflammatory interventions (table 1), 7 of which are repurposed drugs (e.g., antiviral, antibiotic, and rheumatoid arthritis medications) and 1 is a biologic (plasma).⁶

It is worth emphasizing a few recent efforts that target specific aspects of inflammation. For example, GC021109, which was shown to be safe in a phase 1 trial of patients with AD, promotes microglial phagocytosis by binding to the microglial P2Y6 receptor.^{13,14} Other approaches attempt to reduce microglial cytokine production. The NLRP3 inflammasome is a multi-protein complex involved with the innate immune system and activates procaspase-1, which in turn induces production of

proinflammatory cytokines IL-1 β and IL-18.⁸ The NLRP3 inflammasome significantly contributes to neuroinflammation and age-related cognitive decline and is potently activated by A β .¹⁵ Novel compounds that specifically inhibit the NLRP3 inflammasome are currently under development, with companies such as IFM Therapeutics (Boston, MA) expecting to have NLRP3 inhibitors for AD in clinical studies by 2020 (ifmthera.com/pipeline/). Resolution is the final stage of the inflammatory response when immune cells, apoptotic cells, and debris are cleared from the site of insult and proinflammatory mediators are catabolized such that the tissue can reach functional homeostasis.¹⁶ With chronic inflammation, there is incomplete resolution of the initial response, resulting in chronic and increased levels of tumor necrosis factors, interferons, and IL-6. Instead of globally inhibiting inflammation, it may be fruitful to promote resolution of inflammation by using specialized proresolving mediators.¹⁷

Senescent cells are thought to fuel aging and age-related pathologies as they release proinflammatory cytokines, chemokines, and tissue-damaging proteases and can negatively affect the surrounding tissue microenvironment.¹⁸ Senolytic drugs are drawing attention as they selectively induce apoptosis of these senescent cells. While senolytic drugs appear to provide beneficial effects in rodent models of aging, they may also be associated with slowed wound healing.¹⁹ Further work is needed to establish a causal link between senescent cell accumulation and AD before these drugs can be translated into the clinic. In addition, drugs targeting specific phenotypes of myeloid cells or select elements of the complement pathway are in preclinical and clinical development.^{20,21} It is critical that these agents inhibit the detrimental aspects of inflammation while preserving the defense mechanisms against pathogens and tissue damage and allowing for continued phagocytosis by microglia.

Table 1 Interventions targeting inflammation that are in clinical development for Alzheimer disease (as of July 1, 2017⁶)

Intervention	Mechanism of action	Phase	Sponsor
ALZT-OP1	Cromolyn sodium + ibuprofen	Phase 3	AZTherapies, Inc., PharmaConsulting Group, KCAS Bio, APCER Life Sciences
Azeliragon	RAGE inhibitor	Phase 3	vTv Therapeutics
CSP-1103	Microglia activator	Phase 2	CereSpir
Etanercept	Tumor necrosis factor- α inhibitor	Phase 2	University of Southampton
GC021109	P2Y6 agonist	Phase 1	GliaCure, Inc.
Masitinib	Tyrosine kinase inhibitor	Phase 3	AB Science
Minocycline	Tetracycline antibiotic	Phase 2	King's College London
NP001	Sodium chlorite; regulator of inflammatory monocytes/macrophages	Phase 1	Neuraltus Pharmaceuticals, Inc.
Plasma	Nonspecific	Phase 1	Stanford University, Alkahest, Inc.
Sargramostim	Granulocyte colony stimulator	Phase 2	University of Colorado, Denver, The Dana Foundation
Valaciclovir	Antiviral	Phase 2	Hugo Lovheim, Umeå University
VX-745	p38 mitogen-activated protein kinase inhibitor	Phase 2	EIP Pharma, LLC

Impairment in autophagy and clearance of misfolded proteins

Autophagy is a process that involves the degradation and recycling of damaged/aggregated proteins, lipids, and larger cellular components including organelles. Autophagic activity decreases with aging, and genes that promote autophagy have been associated with increased lifespan in model organisms.²² In AD models, impaired autophagy is tightly linked to the accumulation of plaques and tangles. Since A β and tau are not the only proteins that misfold or form toxic aggregates in the aging brain, broadly promoting or restoring the impaired autophagic mechanisms may be a more parsimonious way to prevent accumulations of the many various damaged proteins that occur with aging.²³ Nilotinib, a Food and Drug Administration (FDA)-approved drug for the treatment of adult chronic myeloid leukemia, is currently being tested in a phase 2 trial in AD.²⁴ Nilotinib boosts the autophagic machinery by increasing levels of parkin, which is an E3 ubiquitin ligase that plays a critical role in ubiquitination and clearance of misfolded and damaged proteins.²⁵ Perhaps the greatest challenge in restoring clearance mechanisms is to concurrently promote each stage of its machinery, from autophagosome biogenesis, lysosomal fusion, to the final degradation of cargos within autolysosomes.²⁶ This is important because simply inducing autophagy would lead to accumulation of autophagosomes and undigested autolysosomes, which can block axonal trafficking and lead to axonal swelling. A combination of drugs may be necessary in restoring this autophagic flux. Additional challenges include off-target effects of agents that promote autophagy as well as the lack of validated assays to measure autophagic flux in humans.²²

Mitochondrial and metabolic dysfunctions

The free radical theory of aging, the idea that free radicals produced in the course of cellular metabolism contribute to aging and degenerative diseases, was first introduced in 1956 by Harman.²⁷ Indeed, mitochondrial dysfunction and oxidative stress increase with aging and are tightly linked to neurodegeneration. High metabolic demands along with low levels of antioxidative defense mechanisms make the brain especially vulnerable to oxidative damage.²⁸ Aging and AD are associated with inefficient mitochondria and an imbalance between pro-oxidants and antioxidants, which in turn, induce oxidative damage to DNA, proteins, and lipids in the brain. To date, antioxidant agents have not been successful in treating AD,²⁹ partly due to their low bioavailability and poor blood-brain barrier penetration. They may also block oxidative signaling that is necessary for normal cellular functioning.

There are 14 interventions targeting mitochondrial or metabolic dysfunctions that are currently in clinical trials for AD (table 2).⁶ Many of these are repurposed drugs and 7 are

antidiabetics. Type 2 diabetes mellitus is a significant risk factor for AD and both diseases share pathologies including insulin resistance and oxidative stress.³⁰ Thus, insulin, its derivatives, and drugs designed to improve insulin sensitivity such as liraglutide and exenatide are currently being tested for AD (table 2).

Agents that specifically target mitochondria to decrease mitochondria-derived reactive oxygen species may also hold promise for preventing neuronal dysfunction and death. For example, CP2 is a cell-permeable tricyclic pyrone that crosses the blood-brain barrier and accumulates in neuronal mitochondria.³¹ It mildly inhibits the mitochondrial complex I, producing a mito-hormetic effect, augmenting respiratory capacity and reducing proton leak in wild-type mice. CP2 also prevents cognitive impairment in mouse models of AD (APP, PS1, and APP/PS1) while reducing amyloid plaques and phosphorylated tau. SS-31 is another example of a compound with mitochondria-specific actions. It is a small peptide that binds to cardiolipin, a lipid exclusively expressed on the inner mitochondrial membrane that plays a structural role in organizing the components of the electron transport chain into supercomplexes for more efficient oxidative phosphorylation.^{32,33} SS-31 also inhibits the opening of the mitochondrial permeability transition pore that forms under mitochondrial stress, which can lead to mitochondrial swelling and apoptosis.³⁴ Preclinical studies have shown that SS-31 prevents anesthesia-induced cognitive impairment and promotes mitochondrial and synaptic health in models of AD.^{34,35} SS-31 (elamipretide) is currently being tested in clinical trials for rare disease indications, including mitochondrial myopathy, Barth syndrome, Leber hereditary optic neuropathy, and Huntington disease (stealthbt.com/clinical). A repurposing opportunity for SS-31 exists for AD.

Vascular dysfunction

Aging is associated with vascular disease, which contributes to vascular cognitive impairment, vascular dementia, and other dementias including AD. Studies have shown that the total burden of vascular pathology correlates with cognitive deficits,³⁶ and 79.9% of people with AD were reported to have vascular pathology at autopsy.³⁷ The brain requires continuous and well-regulated blood flow due to the high energy demand and inability to store energy. Vascular impairment can result in hypoperfusion, dysfunction of the neurovascular unit, oxidative stress, or inflammation, which in turn can lead to endothelial damage, small vessel disease, blood-brain barrier breakdown, demyelination, infarcts, hemorrhages, and cerebral atrophy.³⁸ There are currently 11 clinical trials testing interventions that target the vascular system (table 3), of which 9 are repurposed drugs such as antihypertensives and antihyperlipidemic agents and 2 are omega-3 fatty acids.⁶

While managing vascular risk factors such as hypertension, dyslipidemia, and diabetes is likely to improve long-term brain health and lower dementia risk, additional efforts to target

Table 2 Interventions targeting mitochondrial and metabolic dysfunctions that are in clinical development for Alzheimer disease (as of July 1, 2017⁶)

Intervention	Mechanism of action	Phase	Sponsor
AC-1204	Tricaprilin; ketogenic	Phase 3	Accera, Inc.
Benfotiamine	Vitamin B1 derivative	Phase 2	Burke Medical Research Institute, Burke Rehabilitation Hospital, Columbia University, National Institute on Aging, Alzheimer's Drug Discovery Foundation
Exendin-4	GLP-1 receptor agonist	Phase 2	National Institute on Aging, NIH Clinical Center
Grape seed polyphenolic extract, resveratrol	Antioxidant	Phase 1	Johns Hopkins University, Icahn School of Medicine at Mount Sinai
Insulin aspart	Increased insulin signaling	Phase 1	Wake Forest School of Medicine, National Institute on Aging, General Electric
Insulin detemir	Increased insulin signaling	Phase 2	Wake Forest School of Medicine, Alzheimer's Association
Insulin glulisine	Increased insulin signaling	Phase 2	HealthPartners Institute for Education and Research
Insulin (Humulin R U-100)	Increased insulin signaling	Phase 3	University of Southern California, National Institute on Aging, Alzheimer's Therapeutic Research Institute, Wake Forest School of Medicine
Liraglutide	GLP-1 receptor agonist	Phase 2	Imperial College London, King's College Hospital NHS Trust, University of Oxford, University of Southampton, Avon and Wiltshire Mental Health Partnership NHS Trust
MSDC-0160	mTOD modulator, insulin sensitizer	Phase 2	Metabolic Solutions Development Company
Nicotinamide	Vitamin B3	Phase 2	University of California, Irvine
Oxaloacetate	Intermediate of the Krebs cycle	Phase 1	Russell Swerdlow, MD, University of Kansas Medical Center
Pioglitazone	PPAR- γ agonist	Phase 3	Takeda Pharmaceutical Company, Zinfandel Pharmaceuticals Inc.
T3D-959	PPAR- δ/γ agonist	Phase 2	T3D Therapeutics, Inc.

specific vascular pathobiologies are needed. For example, upon blood–brain barrier disruption or vascular breakdown, fibrinogen leaks into the CNS, resulting in formation of clots comprising insoluble fibrin and inflammation.³⁹ Extravascular fibrin(ogen) then interacts with microglia via the integrin receptor CD11b/CD18, which induces secretion of cytokines and chemokines and stimulates recruitment of peripheral monocytes and macrophages.⁴⁰ While fibrinogen is undetectable in the healthy brain, it is present in the brains of patients with AD as well as in older people without AD pathology.^{41,42} A β also interacts with fibrinogen and coagulation factor XII, which can further increase clotting, fibrin deposition, and proinflammatory molecules.⁴³ Therefore, a higher plasma level of fibrinogen is associated with an increased risk for AD and vascular dementia.⁴⁴ Thrombin, an enzyme in blood plasma that causes blood clotting by converting fibrinogen to fibrin, is also elevated in the brains of patients with AD, and produces proinflammatory effects on endothelial cells, microglia, and astrocytes.⁴⁵ Targeting the coagulation system may reduce fibrin formation, neuroinflammation, and neurodegeneration; however, it is important to specifically target the pathogenic properties of coagulation proteins without affecting the beneficial processes of blood clotting.

Epigenetic changes

Aging is also accompanied by important epigenetic changes including histone modifications, DNA methylation, and microRNA expression, resulting in alterations in gene expression and genome architecture.⁴⁶ As epigenetic mechanisms are critical for normal brain function, including learning and memory processes, epigenetic dysregulations may contribute to the onset of cognitive dysfunction and AD.⁴⁷ Because age- and disease-related epigenetic disturbances are potentially reversible, they have drawn attention as attractive targets for pharmacologic interventions particularly in cancer therapies, but they are also gaining traction in neurodegenerative diseases. There are a few epigenetic drugs currently being tested in clinical trials for AD. Vorinostat, a pan-histone deacetylase (HDAC) inhibitor approved for the treatment of cutaneous T-cell lymphoma, is currently in phase I trial in patients with AD.⁴⁸ ORY-2001 is a selective dual LSD1-MAO-B inhibitor that has shown marked cognitive improvement in transgenic AD models, and phase I results showed safety, tolerability, and brain penetrance.⁴⁹ LSD1 is an epigenetic modulator that regulates histone methylation. The major advantage of epigenetic drugs is that they can regulate expression of multiple

Table 3 Interventions targeting vascular dysfunctions that are in clinical development for Alzheimer disease (as of July 1, 2017⁶)

Intervention	Mechanism of action	Phase	Sponsor
Candesartan	Angiotensin receptor blocker	Phase 2	Emory University
Cilostazol	Phosphodiesterase 3 antagonist	Phase 2	National Cerebral and Cardiovascular Center, Japan
Gemfibrozil	Modulation of microRNA pathways	Phase 1	Gregory Jicha, University of Kentucky
Icosapent ethyl	Eicosapentaenoic acid, a type of omega-3 fatty acid	Phase 3	VA Office of Research and Development, University of Wisconsin, Madison
Nilvadipine	Calcium channel blocker	Phase 3	University of Dublin, Trinity College, Molecular Medicine Ireland LBG, Alzheimer Europe, Archer Pharmaceuticals, Inc., E-Search Limited, University College Dublin, GABO:mi, King's College London, Istituto Di Ricerche Farmacologiche Mario Negri, University Hospital, Lille, University of Ulm, Szeged University, Goeteborgs Universitet, University College Cork, Aristotle University of Thessaloniki, Stichting Katholieke Universiteit
Omega-3 PUFA	Decrease triglycerides, reduce blood clotting	Phase 2	Oregon Health and Science University, National Institute on Aging
Simvastatin	HMG-CoA reductase inhibitor (statin)	Phase 2	University of Wisconsin, Madison, National Institute on Aging
Simvastatin, L-arginine, tetrahydrobiopterin	HMG-CoA reductase inhibitor and antioxidant	Phase 2	University of Massachusetts, Worcester
Tadalafil	PDE5 inhibitor; increases blood flow	Phase 2	St. George's, University of London, Alzheimer's Drug Discovery Foundation, Alzheimer's Society UK, University of Copenhagen, University of Glasgow, St George's University Hospitals NHS Foundation Trust
Telmisartan	Angiotensin 2 receptor antagonist	Phase 1	Emory University
Telmisartan, perindopril	Angiotensin 2 receptor antagonist (Telmisartan) and ACE inhibitor (Perindopril)	Phase 2	Alzheimer's Drug Discovery Foundation, Sunnybrook Health Sciences Centre

genes critical for neuronal functions. However, studies are required to confirm that these drugs aimed to counter neurodegeneration in the brain do not also increase gene expression associated with harm, such as tumorigenesis. Preclinical efforts addressing these safety issues are also underway, including selective inhibitors of HDAC2 that show functional efficacy and reduced side effects in animal models (rodintherapeutics.com/our-approach/#literature).

Synaptic loss and dysfunction

Normal age-related cognitive decline is not accompanied by the extensive neuronal loss seen in AD and other dementias; however, it is associated with dysfunctions and loss of cortical synapses.⁵⁰ These synaptic alterations occur in the same circuits that degenerate in AD. Based on a postmortem study, synapse loss is observed in a large proportion of people with mild cognitive impairment and appears to be an early event in the disease process that precedes neuronal loss in AD.⁵¹ Because age-related synaptic alterations may render neurons more vulnerable to degeneration, maintaining synaptic health in the face of aging may be an important strategy for preventing neurodegeneration.

There is growing interest in therapies that promote neuronal and synaptic health for preventing and treating dementia.

Currently 19 neuroprotective interventions are being tested in clinical trials for AD (table 4), of which 5 are cell therapies (e.g., stem cells), 3 are natural products, and 2 are biologics.⁶ In particular, nerve growth factor signaling has drawn interest as a potential neuroprotective target for AD. LM11A-31-BHS, a small molecule ligand for the p75 neurotrophin receptor (p75^{NTR}), is currently being tested in a phase 2 trial in patients with AD. Treatment with this molecule reversed cholinergic neurite degeneration in AD mouse models even when it was initiated after significant pathology was already present.⁵²

Combination therapies

As discussed above, multiple processes go awry with aging, many of which negatively affect neuronal and cognitive health and ultimately contribute to the onset and progression of AD. Therefore, a combination of drugs to address these systems may be necessary to effectively treat it. There are currently 11 combination therapy clinical trials (table 5), of which 5 are testing an add-on therapy to an already approved AD drug (e.g., donepezil), and several others are using multiple drugs to target A β .⁶ In 2018, a phase 2 clinical trial to test AMX0035, a combination of sodium phenylbutyrate and tauroursodeoxycholic acid (TUDCA), is expected to begin.

Table 4 Neuroprotective interventions that are in clinical development for Alzheimer disease (as of July 1, 2017⁶)

Intervention	Mechanism of action	Phase	Sponsor
Adipose-derived stromal cells	Nonspecific	Phase 2	Ageless Regenerative Institute
Allopregnanolone	GABA-A receptor modulator	Phase 1	University of Southern California, National Institute on Aging
ANAVEX2-73	Sigma1/muscarinic receptor agonist	Phase 2	Anavex Life Sciences Corp.
AstroStem	Autologous fat stem cells; nonspecific	Phase 2	Nature Cell Co. Ltd.
AZD0530	Src tyrosine kinase inhibitor	Phase 2	Yale University, Alzheimer's Therapeutic Research Institute
Bryostatin 1	Protein kinase C modulator	Phase 2	Neurotrope Bioscience, Inc.
CB-AC-02	Placenta-derived mesenchymal stem cells; nonspecific	Phase 2	CHABiotech Co., Ltd.
CT1812	Sigma2 receptor antagonist	Phase 2	Cognition Therapeutics
GV1001	Telomerase reverse transcriptase vaccine	Phase 2	GemVax & Kael
L-Serine	Amino acid	Phase 2	Dartmouth-Hitchcock Medical Center, Brain Chemistry Laboratories, Institute for Ethnomedicine
LM11A-31	p75 neurotrophin receptor agonist	Phase 2	Pharmatrophix
Mesenchymal stem cells (allogenic)	Nonspecific	Phase 2	Stemmedica Cell Technologies, Inc., Stemmedica International SA
Mesenchymal stem cells (umbilical cord)	Nonspecific	Phase 2	South China Research Center for Stem Cell and Regenerative Medicine, Third Affiliated Hospital, Sun Yat-Sen University, Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, Guangzhou Psychiatric Hospital
MLC901	Ingredients from natural products; nonspecific	Phase 2	National University Hospital, Singapore
Rasagiline	Monoamine oxidase B inhibitor	Phase 2	The Cleveland Clinic
S-Equol	Estrogen receptor β agonist	Phase 2	Russell Swerdlow, MD, Ausio Pharmaceuticals, LLC, University of Kansas Medical Center
STA-1, donepezil	Antioxidant (echinacoside)	Phase 2	Sinphar Pharmaceutical Co., Ltd.
T-817 MA	Sigma receptor activator, neurotrophic	Phase 2	Toyama Chemical Co., Ltd., Alzheimer's Disease Cooperative Study
Xanamem	11-HSD1 enzyme activity blocker	Phase 2	Actinogen Medical, ICON Clinical Research

Sodium phenylbutyrate is an FDA-approved therapy for urea cycle disorders and it is a Class I and II HDAC inhibitor. Preclinical studies have shown that it also acts as a chemical chaperone and ameliorates ER stress, prevents neuronal loss, increases clearance of intraneuronal A β , and restores cognitive functions in AD mouse models.⁵³⁻⁵⁵ TUDCA is a bile acid that supports mitochondrial energetics by reducing mitochondrial permeability and increasing apoptotic thresholds of cells.⁵⁶ Studies in an AD mouse model (APP/PS1) have shown that TUDCA decreases A β deposits, reduces glial activation, and restores cognitive functions.^{57,58} Together, the 2 drugs are designed to restore epigenetic changes, reduce cellular stress, and protect against neurodegeneration, mitochondrial dysfunction, and neuroinflammation.

Combination trials present some challenges as each drug needs to be tested for safety, and multiple biomarkers are often required to ensure target engagement and to monitor disease progression and response to treatment. Some evidence of efficacy should be demonstrated for each drug, though benefits of each may be incremental. Combination therapies that target multiple age-related dysfunctions with synergistic activities are especially promising for treating AD. More such combination studies are needed.

Future directions

Biological aging is the leading risk factor for the major debilitating chronic diseases of old age that cause morbidity and

mortality, including AD and other dementias. Drugs that treat fundamental biological mechanisms of aging have been proposed to be useful for most prevalent chronic diseases of aging.¹⁸ In fact, many repurposed drugs are used to treat other age-related diseases. Despite over 75 years of accumulated research on biological aging,⁵⁹ the current drug development pipeline is dominated by therapeutics targeting A β and tau, and there has been proportionately less translation of biological gerontology into our efforts to develop drugs for AD. Nevertheless, aging biology provides numerous novel targets for new drug development for AD (figure).

Because of the multifaceted nature of biological aging, it is unlikely that drugs addressing a single target will be very successful in effectively treating AD. Nevertheless, single drug clinical trials may be needed to demonstrate incremental benefits, even if modest, before combination trials can be pursued. As interventions that target one aberrant system tend to also attenuate others, ultimately, combination therapies that target multiple age-related dysfunctions may produce synergistic activities. Combination therapies are already the standard of care for other diseases of aging, including heart disease, cancers, and hypertension, and will likely be necessary in treating AD and other dementias. And because the same biological aging mechanisms underpin the common diseases of aging, repurposing drugs already on the market is a rational

strategy for testing new therapies for AD and related dementias, including the sporadic forms of frontotemporal dementia and vascular dementia. Novel therapeutics for new and relevant targets will clearly also be needed.

In addition to combination therapies, addressing the multifaceted nature of the relationship between biological aging and AD with drugs possessing pleiotropic effects (simultaneously producing more than one effect) will be advantageous. In clinical areas such as oncology, psychiatry, and cardiovascular medicine, many effective drugs act on multiple targets while single-targeted approaches seldom progress to the final stages of clinical trials.⁶⁰ For example, statins are widely used to lower cholesterol levels in patients with dyslipidemia, but statins also have pleiotropic effects that are independent of their effects on cholesterol, including improved endothelial function, inhibition of vascular inflammation, stabilization of atherosclerotic plaques, and immunomodulation.⁶⁰ To effectively treat AD, pleiotropic drugs may need to hit the right nodes of relevant biological networks affected by aging such that they positively influence those networks and interconnected pathways.

Finally, a parsimonious approach to drug discovery and development with regard to translating knowledge from biological aging to AD is needed. For example, due to the plethora of misfolded proteins that accumulate with aging in the brain,

Table 5 Combination therapies that are in clinical development for Alzheimer disease (as of July 1, 2017⁶)

Intervention	Mechanism of action	Phase	Sponsor
ALZT-OP1	Cromolyn sodium + ibuprofen	Phase 3	AZTherapies, Inc., PharmaConsulting Group, KCAS Bio, APCER Life Sciences
CNP520, CAD106	BACE1 inhibitor + anti-amyloid antibody	Phase 3	Novartis Pharmaceuticals, Banner Alzheimer's Institute, National Institute on Aging, Alzheimer's Association, Amgen
CPC-201	Donepezil (acetylcholinesterase inhibitor) + a peripherally acting cholinergic blocker	Phase 2	Chase Pharmaceuticals Corporation
DHP1401, donepezil	AMPA receptor and MAP kinase modulation + donepezil	Phase 2	Daehwa Pharmaceutical Co., Ltd.
Gantenerumab, solanezumab	Antibody against A β fibrils + antibody against soluble monomeric A β	Phase 3	Washington University School of Medicine, Eli Lilly and Company, Hoffmann-La Roche, Alzheimer's Association, National Institute on Aging, Avid Radiopharmaceuticals, Accelerating Medicines Partnership
Grape seed polyphenolic extract, resveratrol	Antioxidant	Phase 1	Johns Hopkins University, Icahn School of Medicine at Mount Sinai
Lu AE58054, memantine	5-HT ₆ receptor antagonist + memantine (NMDA receptor blocker)	Phase 3	H. Lundbeck A/S, Otsuka Pharmaceutical
PXT00864	Acamprosate (NMDA receptor antagonist/positive allosteric modulator of GABA-A receptors) + baclofen (GABA-B receptor agonist)	Phase 2	Pharnext SA, Ascopharm Groupe Novasco
Simvastatin, L-arginine, tetrahydrobiopterin	HMG-CoA reductase inhibitor and antioxidant	Phase 2	University of Massachusetts, Worcester
STA-1, donepezil	Antioxidant (echinacoside) + donepezil	Phase 2	Sinphar Pharmaceutical Co., Ltd.
TAK-071, donepezil	Muscarinic M1R positive allosteric modulator + donepezil	Phase 1	Takeda Pharmaceutical Co., Ltd.

biologics that attempt to address a single misfolded protein may be far less efficacious than drugs that enhance autophagy and clearance of all misfolded proteins. Similarly, age-related inflammation, vascular disease, epigenetic dysregulation, mitochondrial/metabolic dysfunction, and synaptic failure may be upstream causes of neuronal dysfunction and death leading to the classic pathologic hallmarks that have been historically among the first drug targets in AD. A better understanding and translation of the systemic, cellular, and molecular processes of biological aging that precede and increase vulnerability to AD will help identify new strategies and therapeutic targets for drug discovery and development.

Study funding

This work was supported by a donation to the Alzheimer's Drug Discovery Foundation by an anonymous foundation. Alzheimer's Drug Discovery Foundation has funded or cofunded several projects to develop or clinically test the following drugs that are discussed in the article: nilotinib, CP2, GC021109, LM11A-31, and ORY-2001.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* June 14, 2018. Accepted in final form August 23, 2018.

Appendix 1 Author table

Name	Location	Role	Contribution
Yuko Hara, PhD	Alzheimer's Drug Discovery Foundation	Author	Drafted and revised the manuscript for intellectual content
Nicholas McKeenan, BS	Alzheimer's Drug Discovery Foundation	Author	Revised the manuscript for intellectual content
Howard M Fillit, MD	Alzheimer's Drug Discovery Foundation	Author	Drafted and revised the manuscript for intellectual content

References

- Kennedy BK, Berger SL, Brunet A, et al. Geroscience: linking aging to chronic disease. *Cell* 2014;159:709–713.
- Ricklefs RE, Scheuerlein A. Biological implications of the Weibull and Gompertz models of aging. *J Gerontol A Biol Sci Med Sci* 2002;57:B69–B76.
- Anderson RM, Le Couteur DG. A long tradition in advancing aging biology and translational gerontology. *J Gerontol A Biol Sci Med Sci* 2018;73:271–272.
- Gonneaud J, Arenaza-Urquijo EM, Mezenge F, et al. Increased florbetapir binding in the temporal neocortex from age 20 to 60 years. *Neurology* 2017;89:2438–2446.
- Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer disease. *Nat Rev Neurol* 2018;14:399–415.
- Alzheimer's Drug Discovery Foundation 2017. Closing in on a Cure: 2017 Alzheimer's Clinical Trials Report. Available at: alzdiscovery.org/research-and-grants/clinical-trials-report/closing-in-on-a-cure-2017. Accessed July 26, 2018.
- Shih HP, Zhang X, Aronov AM. Drug discovery effectiveness from the standpoint of therapeutic mechanisms and indications. *Nat Rev Drug Discov* 2018;17:19–33.
- Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci* 2014;69(suppl 1):S4–S9.
- Corlier F, Hafzalla G, Faskowitz J, et al. Systemic inflammation as a predictor of brain aging: contributions of physical activity, metabolic risk, and genetic risk. *Neuroimage* 2018;172:118–129.

- Warren KN, Beason-Held LL, Carlson O, et al. Elevated markers of inflammation are associated with longitudinal changes in brain function in older adults. *J Gerontol A Biol Sci Med Sci* 2018;73:770–778.
- Marsland AL, Gianaros PJ, Kuan DC, Sheu LK, Krajina K, Manuck SB. Brain morphology links systemic inflammation to cognitive function in midlife adults. *Brain Behav Immun* 2015;48:195–204.
- Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol* 2015;14:388–405.
- Study evaluating safety, tolerability, and PK of multiple ascending doses of GC021109 in subjects with mild to moderate Alzheimer's disease. 2015. Available at: clinicaltrials.gov/ct2/show/study/NCT02386306. Accessed July 26, 2018.
- GC 021109. Alzforum. Available at: alzforum.org/therapeutics/gc-021109. Accessed July 26, 2018.
- Goldberg EL, Dixit VD. Drivers of age-related inflammation and strategies for healthspan extension. *Immunol Rev* 2015;265:63–74.
- Fullerton JN, Gilroy DW. Resolution of inflammation: a new therapeutic frontier. *Nat Rev Drug Discov* 2016;15:551–567.
- Serhan CN, Chiang N, Dalli J. The resolution code of acute inflammation: novel pro-resolving lipid mediators in resolution. *Semin Immunol* 2015;27:200–215.
- Kirkland JL, Tchkonja T, Zhu Y, Niedernhofer LJ, Robbins PD. The clinical potential of senolytic drugs. *J Am Geriatr Soc* 2017;65:2297–2301.
- Baker DJ, Petersen RC. Cellular senescence in brain aging and neurodegenerative diseases: evidence and perspectives. *J Clin Invest* 2018;128:1208–1216.
- Biber K, Moller T, Boddeke E, Prinz M. Central nervous system myeloid cells as drug targets: current status and translational challenges. *Nat Rev Drug Discov* 2016;15:110–124.
- Brennan FH, Lee JD, Ruitenber MJ, Woodruff TM. Therapeutic targeting of complement to modify disease course and improve outcomes in neurological conditions. *Semin Immunol* 2016;28:292–308.
- Rubinsztein DC, Marino G, Kroemer G. Autophagy and aging. *Cell* 2011;146:682–695.
- Boyle PA, Yang J, Yu L, et al. Varied effects of age-related neuropathologies on the trajectory of late life cognitive decline. *Brain* 2017;140:804–812.
- Turner RS. Impact of nilotinib on safety, biomarkers and clinical outcomes in mild to moderate Alzheimer's disease (AD). 2016. Available at: clinicaltrials.gov/ct2/show/NCT02947893. Accessed July 26, 2018.
- Lonskaya I, Hebron ML, Desforges NM, Schachter JB, Moussa CE. Nilotinib-induced autophagic changes increase endogenous parkin level and ubiquitination, leading to amyloid clearance. *J Mol Med* 2014;92:373–386.
- Friedman LG, Qureshi YH, Yu WH. Promoting autophagic clearance: viable therapeutic targets in Alzheimer's disease. *Neurotherapeutics* 2015;12:94–108.
- Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 1956;11:298–300.
- Jovanovic Z. Antioxidative defense mechanisms in the aging brain. *Arch Biol Sci* 2014;66:245–252.
- Galasko DR, Peskind E, Clark CM, et al. Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. *Arch Neurol* 2012;69:836–841.
- Sebastiao I, Candeias E, Santos MS, de Oliveira CR, Moreira PI, Duarte AI. Insulin as a bridge between type 2 diabetes and Alzheimer disease: how anti-diabetics could be a solution for dementia. *Front Endocrinol* 2014;5:110.
- Zhang L, Zhang S, Maezawa I, et al. Modulation of mitochondrial complex I activity averts cognitive decline in multiple animal models of familial Alzheimer's Disease. *EBioMedicine* 2015;2:294–305.
- Birk AV, Liu S, Soong Y, et al. The mitochondrial-targeted compound SS-31 re-energizes ischemic mitochondria by interacting with cardiolipin. *J Am Soc Nephrol* 2013;24:1250–1261.
- Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. *Br J Pharmacol* 2014;171:2029–2050.
- Wu J, Zhang M, Li H, et al. BDNF pathway is involved in the protective effects of SS-31 on isoflurane-induced cognitive deficits in aging mice. *Behav Brain Res* 2016;305:115–121.
- Calkins MJ, Manczak M, Reddy PH. Mitochondria-targeted antioxidant SS31 prevents amyloid beta-induced mitochondrial abnormalities and synaptic degeneration in Alzheimer's disease. *Pharmaceuticals* 2012;5:1103–1119.
- Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:2672–2713.
- Toledo JB, Arnold SE, Raible K, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain* 2013;136:2697–2706.
- Iadecola C. The pathobiology of vascular dementia. *Neuron* 2013;80:844–866.
- Bardehle S, Rafalski VA, Akassoglou K. Breaking boundaries-coagulation and fibrinolysis at the neurovascular interface. *Front Cell Neurosci* 2015;9:354.
- Ryu JK, Petersen MA, Murray SG, et al. Blood coagulation protein fibrinogen promotes autoimmunity and demyelination via chemokine release and antigen presentation. *Nat Commun* 2015;6:8164.
- Ryu JK, McLarnon JG. A leaky blood-brain barrier, fibrinogen infiltration and microglial reactivity in inflamed Alzheimer's disease brain. *J Cell Mol Med* 2009;13:2911–2925.
- Viggars AP, Wharton SB, Simpson JE, et al. Alterations in the blood brain barrier in ageing cerebral cortex in relationship to Alzheimer-type pathology: a study in the MRC-CFAS population neuropathology cohort. *Neurosci Lett* 2011;505:25–30.

43. Ahn HJ, Chen ZL, Zamolodchikov D, Norris EH, Strickland S. Interactions of beta-amyloid peptide with fibrinogen and coagulation factor XII may contribute to Alzheimer's disease. *Curr Opin Hematol* 2017;24:427–431.
44. van Oijen M, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Fibrinogen is associated with an increased risk of Alzheimer disease and vascular dementia. *Stroke* 2005;36:2637–2641.
45. Grammas P, Martinez JM. Targeting thrombin: an inflammatory neurotoxin in Alzheimer's disease. *J Alzheimers Dis* 2014;42(suppl 4):S537–S544.
46. Brunet A, Berger SL. Epigenetics of aging and aging-related disease. *J Gerontol A Biol Sci Med Sci* 2014;69(suppl 1):S17–S20.
47. Delgado-Morales R, Agis-Balboa RC, Esteller M, Berdasco M. Epigenetic mechanisms during ageing and neurogenesis as novel therapeutic avenues in human brain disorders. *Clin Epigenetics* 2017;9:67.
48. Kuhrs S. Clinical trial to determine tolerable doses of vorinostat in patients with mild Alzheimer disease (VostatAD01). 2017. clinicaltrials.gov/ct2/show/NCT03056495. Accessed July 26, 2018.
49. Maes T, Molinero C, Antonijoan RM, et al. First-in-human phase I results show safety, tolerability and brain penetrance of ORY-2001, an epigenetic drug targeting LSD1 and MAO-B. *Alzheimers Dement* 2017;13:P1573–P1574.
50. Morrison JH, Baxter MG. The ageing cortical synapse: hallmarks and implications for cognitive decline. *Nat Rev Neurosci* 2012;13:240–250.
51. Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging* 2006;27:1372–1384.
52. Simmons DA, Knowles JK, Belichenko NP, et al. A small molecule p75NTR ligand, LM11A-31, reverses cholinergic neurite dystrophy in Alzheimer's disease mouse models with mid- to late-stage disease progression. *PLoS One* 2014;9:e102136.
53. Cuadrado-Tejedor M, Ricobaraza AL, Torrijo R, Franco R, Garcia-Osta A. Phenylbutyrate is a multifaceted drug that exerts neuroprotective effects and reverses the Alzheimer's disease-like phenotype of a commonly used mouse model. *Curr Pharm Des* 2013;19:5076–5084.
54. Ricobaraza A, Cuadrado-Tejedor M, Garcia-Osta A. Long-term phenylbutyrate administration prevents memory deficits in Tg2576 mice by decreasing Abeta. *Front Biosci* 2011;3:1375–1384.
55. Ricobaraza A, Cuadrado-Tejedor M, Marco S, Perez-Otano I, Garcia-Osta A. Phenylbutyrate rescues dendritic spine loss associated with memory deficits in a mouse model of Alzheimer disease. *Hippocampus* 2012;22:1040–1050.
56. Rodrigues CM, Sola S, Brito MA, Brondino CD, Brites D, Moura JJ. Amyloid beta-peptide disrupts mitochondrial membrane lipid and protein structure: protective role of tauroursodeoxycholate. *Biochem Biophys Res Commun* 2001;281:468–474.
57. Dionisio PA, Amaral JD, Ribeiro MF, Lo AC, D'Hooge R, Rodrigues CM. Amyloid-beta pathology is attenuated by tauroursodeoxycholic acid treatment in APP/PS1 mice after disease onset. *Neurobiol Aging* 2015;36:228–240.
58. Nunes AF, Amaral JD, Lo AC, et al. TUDCA, a bile acid, attenuates amyloid precursor protein processing and amyloid-beta deposition in APP/PS1 mice. *Mol Neurobiol* 2012;45:440–454.
59. Frank LK. *Gerontology*. *J Gerontol* 1946;1:1–12.
60. Banfi C, Baetta R, Gianazza E, Tremoli E. Technological advances and proteomic applications in drug discovery and target deconvolution: identification of the pleiotropic effects of statins. *Drug Discov Today* 2017;22:848–869.

Neurology® Online CME Program

Earn CME while reading *Neurology*. This program is available only to online *Neurology* subscribers. Read the articles marked CME, go to Neurology.org, and click on CME. This will provide all of the information necessary to get started. The American Academy of Neurology (AAN) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. *Neurology* is planned and produced in accordance with the ACCME Essentials. For more information, contact AAN Member Services at 800-879-1960.

Sign Up for the AAN's Axon Registry

The AAN encourages its US members to show their interest in participating in the Axon Registry® by signing up today.

Use the Axon Registry to:

- Simplify reporting requirements under MACRA's Quality Payment Program and avoid penalties while reducing your administrative burden
- Meet your MOC Part IV requirements and waive up to eight credits of Part II Self-Assessment
- Choose from 22 AAN neurology-specific quality measures that fit your practice
- Use data to understand your practice and identify where improvements can be made to patient care
- Manage your patients at a population level; look at a specific group of patients based on conditions, risk factors, demographics or outcome
- Demonstrate your value to payers when negotiating reimbursement
- Enjoy multi-year, fee-free access when you sign the agreements and integrate your EHR with the registry

Learn more at AAN.com/view/Axon and send your questions to registry@aan.com.
