Alzheimer's Disease: Research Priorities

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As many as 5.1 million Americans may have Alzheimer's Disease, a figure that is expected to triple to nearly 13.8 million by 2050. While there currently is no cure for AD, researchers are optimistic that effective treatments are on the horizon.

Alzheimer's Disease: Research Priorities is a recently published series of articles that brings you the stories behind the research and celebrates the researchers and organizations committed to improving health care. Please accept this complimentary copy as our way of thanking you for your commitment to advancing medicine and improving patients' lives.

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Alzheimer's Disease and the Central Nervous System

The Central Nervous System: A Brief Primer

By Emily Burke, Ph.D., Director of Curriculum Development, BiotechPrimer.com

The central nervous system (CNS) consists of the brain and the spinal cord. It sends and receives information from the peripheral nervous system—the vast network of nerves that feed into every tissue of the body. These signals enable voluntary and involuntary movement, and allow the brain to process and interpret sensory information sent from the spinal cord.

Specialized cells called neurons make up the CNS. Neurons send and receive signals electrochemically, meaning a chemical message is converted into an electrical signal within the neuron. When a chemical message (a neurotransmitter) reaches the edge of the neuron (the dendrite) the neurotransmitter causes ion channels in the cell membrane to open. This action allows positively charged sodium ions to enter sending a charge—an electrical signal—through the body of the neuron. The charge leaves through the neuron's opposite side, another extension called an axon. This release causes other neurotransmitters to activate other neurons. Different neurons send and receive different types of neurotransmitters. Billions of neurons within the central nervous system communicate via 100+ different types of neurotransmitters. This neuron/neurotransmitter dual regulates just about everything within the human body from movement, to hunger, to body temperature, to emotion, and to wakefulness.

Not surprisingly, such a complex system—and the various diseases that affect it—are not entirely understood. Conditions that impact the CNS include infectious disease, genetic disease, cancer, stroke, and traumatic injury. In the next few paragraphs, we'll take a closer look at four CNS diseases that are top research priorities.

Huntington's Disease (HD)

Huntington's disease (HD) is a neurodegenerative disorder— neurons progressively lose structure and function. As the disease continues and more neurons are damaged and die, symptoms get worse. Early stage patients may experience subtle involuntary movements and mood disturbances, but as the disease progresses, patients lose the ability to walk, speak, and swallow. Life expectancy is 20 years after onset of initial symptoms. 90 percent of HD cases affect adults between the ages of 30 and 50; juvenile onset occurs in the remaining 10 percent of cases.

HD is a monogenic disease, meaning it is caused by a mutation in one gene, dubbed the Huntington

gene. The disease is also dominant. Everyone has two copies of each gene; for dominant genetic diseases, one mutated copy ensures the person will develop the disease, even if the other copy is correct. In practical terms, this means if an individual's parent had HD, that individual has a 50 percent chance of developing it themselves. Because there is currently no cure for HD, some at-risk individuals may choose not to be tested for the gene. In fact, HD testing of people younger than 18 is prohibited, unless they are already showing symptoms of juvenile onset HD. This moratorium is to ensure that those tested understand the full implications.

Despite knowing the genetic basis of HD, scientists do not yet fully understand the disease mechanism. Recent advances in gene therapy and genome editing (fixing defective gene copies with functional copies) offer new hope for an HD cure. Replacing dead or damaged neurons with new neurons derived from stem cells is another approach under investigation.

Parkinson's Disease

Like HD, Parkinson's disease (PD) is a neurodegenerative disorder. In particular, PD patients have reduced activity and death of neurons that secrete the neurotransmitter dopamine. Typical symptoms of PD include motor disturbances such as tremors, slowness of movement, and rigidity, as well as a decline in cognitive function. Since PD primarily affects people over 60, as the Baby Boomer population ages, significant increases in PD are expected.

Parkinson's is not a genetic disorder in the same sense that HD is—there is not a specific gene associated with it. In fact, the majority of cases are classified as "sporadic," in other words, arising without a genetic association or apparent cause. Ongoing research into the disease involves teasing out genes that may indicate increased susceptibility. There is currently no cure for PD; however drugs that mimic the effect of dopamine have proven successful at managing some of the motor disturbances. Ongoing research also involves using stem cell-derived neuronal cells to replace dead or dying neurons.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease in which the patient's own immune system attacks and destroys the protective insulating layer known as the myelin sheath that surrounds the axon section of the neuron. This lack of myelin results in problems with the transmission of electrical signals from one neuron to the next.

MS typically strikes people in their early adult years. Initial symptoms vary widely, as they are dependent on the particular part of the CNS that is under attack, which can include motor, sensory, or visual problems. Initial symptoms are often highly intermittent, and might not reoccur for years. MS is a chronic, progressive disease, with symptoms gradually worsening over decades. Advanced patients are often confined to a wheelchair.

Like PD, there is no clear-cut genetic cause, although some genes have been identified as

susceptibility genes, or genes that increase the odds of an individual developing MS. It is more common in women by a three to one ratio; this suggests that hormones play a role in susceptibility as well. Geography is also a factor—there is a higher incidence of cases the farther north one travels from the equator. Since sunlight is required for the sufficient production of vitamin D, it's speculated that vitamin D may play a protective role in susceptible individuals. Likewise, in some cases it is thought that viral infections may trigger MS. The ultimate expression of the disease is likely the result of a combination of genetic and environmental factors.

Although there is no cure for MS, there are a number of drugs on the market that slow down its progression by blunting the immune system's attack on the CNS.

Alzheimer's Disease

Alzheimer's disease (AD) accounts for approximately 70 percent of dementia cases. Like HD and PD, it is a neurodegenerative disease, with neurons in the hippocampal region of the brain associated with memory formation being among the first affected. By 2025, the number of people age 65 and older with Alzheimer's disease is projected to reach 7.1 million—a 40 percent increase from the 5.1 million affected in 2015 (Alzheimer's Association). Alzheimer's disease is associated with the build-up of amyloid-beta (Aß) plaques in patients' brains. But what, exactly, are Aß plaques? Aß plaques derive from the cleavage of a protein called the amyloid precursor protein, which is thought to play a role in the formation of synapses. Individual Aß molecules clump together to form the plaques associated with Alzheimers'.

Until very recently, the mechanism by which Aß plaques might cause Alzheimer's was not known. Researchers at Stanford School of Medicine have recently demonstrated that Aß binds to a receptor on nerves cells that disrupts the function of synapse. This finding suggests a potential drug target: the ability to disrupt this interaction could
preserve functioning nerve cells.

There is currently no cure for AD; however a number of different companies are
working to develop treatments, with a few already in clinical trials. These potential treatments and the basic science that drives them will be covered in a future post.

To read this article on Real World Health Care, click here.

National Institute on Aging Outlines Alzheimer's Priorities

As part of our series on Alzheimer's Disease, Real World Health Care spoke with Creighton Phelps, Ph.D., acting director, Division of Neuroscience, National Institute on Aging, National Institutes of Health. Dr. Phelps discusses the challenges facing AD researchers and how the NIA is working to overcome them.

Real World Health Care: In terms of comparative effectiveness research for Alzheimer's disease, where is the NIA focusing its efforts and why?

Creighton Phelps: Currently, because we do not have treatments to delay or prevent Alzheimer's, comparative effectiveness research is not really an option. That said, Alzheimer's disease is a complicated disorder and we are funding research into genetic, behavioral, and environmental factors that may all play a role in disease onset and progression. As a result, not one, but many interventions may be needed. For this reason, we can't leave any stone unturned. NIA is funding drug-discovery projects, trials using pharmacological interventions, preventative lifestyle interventions, and caregiving interventions.

RWHC: What are some of the biggest challenges researchers and industry face in developing AD therapies?

CP: Clinical trials focused on finding a prevention or cure are imperative to Alzheimer's disease and related dementias research. But a big challenge is that it is often difficult to recruit participants into trials. We need participants with cognitive impairments, as well as those without; we need ethnic minorities; we need people age 65 and older, and also younger adults. This point of comparison helps us to determine which changes in the brain are specifically related to Alzheimer's disease and which can be attributed to aging. Increased participation in clinical trials will really hasten our search for effective therapies. Additionally, participants with dementia need a study partner to assist the participants during the trial, which adds another level of burden for families and loved ones. But without the generous participation of clinical trials volunteers, we won't find a cure for Alzheimer's.

RWHC: How is the NIA helping to overcome these challenges?

CP: NIA is working hard to overcome these and other challenges, and we are grateful that both public and private organizations, and the general public, also place a high priority on dementia research.

Congress just boosted federal funding for Alzheimer's disease and related dementias research by $350 million dollars. It is anticipated that this increased budget will accelerate investigator-initiated discovery after years of smaller budget increases. The budget increase will enable new, highly collaborative initiatives.

In 2011, President Obama signed into law the National Alzheimer's Project Act. This called for the creation and maintenance of an integrated National Plan to overcome Alzheimer's, with the ultimate goal being to find a prevention or cure by year 2025. As mandated in the National Plan, NIA hosted Alzheimer's Disease Summits in 2012 and 2015, bringing experts from pharma, academia, and advocacy groups together to advance the research agenda. NIA also worked with the National Institute of Neurological Disorders and Stroke to hold two Alzheimer's Disease-Related Dementias Summits in 2013 and 2016 to examine the issues central to the other dementias that sometimes overlap with Alzheimer's.

This spirit of collaboration can also be seen in the groundbreaking Accelerating Medicines Partnership (AMP). AMP is a bold new venture among the NIH, 10 biopharmaceutical companies, and several nonprofit organizations that aims to transform the current model for developing new diagnostics and treatments for chronic diseases. AMP-AD, which applies this innovative model to Alzheimer's disease, will enable the rapid sharing of large biomedical datasets that may lead to speedier discovery of therapeutic targets.

RWHC: Can you please provide an overview of some of the more promising therapeutic targets (particularly those moving out of the lab and into human studies) on which the NIA is focused? Where you can, please explain why those have become a priority.

CP: NIA is funding, often in collaboration with others, prevention trials testing drugs that may clear amyloid protein—a hallmark of the disease—in cognitively normal volunteers at high risk for developing the disease due to genetics or who show abnormal amyloid levels in their brains, as visualized by PET Scans. The hope is that by treating the disorder earlier in the disease process that we may delay or even prevent the disease.

RWHC: Where does the NIA see the greatest need for research into Alzheimer's disease: diagnosis, symptom management, stopping/slowing the progression of the disease, or prevention of AD? Why?

CP: Currently, about 5.2 million Americans age 65 and older are living with Alzheimer's disease; many thousands more are diagnosed with related disorders, such as Lewy body or frontotemporal dementia. An even greater number are in the pre-symptomatic stages, sometimes called Mild Cognitive Impairment (MCI) or prodromal disease. These numbers are expected to more than double by 2050 unless we find one or more treatments. Alzheimer's and other forms of dementia are expected to cost the United States $236 billion this year. Of course, the ultimate goal is to treat and prevent the disease. But these staggering statistics reveal that any discoveries—whether in diagnosis, symptom management, stopping/slowing disease progression, or preventing the disease—could help the millions currently afflicted.

RWHC: Besides translational and comparative effectiveness research, what other initiatives does the NIA support in relation to Alzheimer's disease? Any highlights to share in terms of non-pharmacological intervention research?

CP: With these additional financial resources, we are able to fund many new and exciting projects. The additional $350 million will enable: the development of new human cellular models of Alzheimer's that may enable rapid screening of hundreds of thousands of molecules as potential therapeutic agents. It will also allow us to establish translational centers that will develop and apply cutting-edge approaches to drug discovery and development. Other upcoming projects include population studies of trends in the incidence and prevalence of dementia, the development of novel interventions to support dementia caregivers, and clinical trials of therapies in people at the highest risk of dementia.

To read this article on Real World Health Care, click here.

BrightFocus Foundation Leaving No Stone Unturned in Fight against Alzheimer's

This week, Real World Health Care talks with Diane Bovenkamp, Ph.D., Chief Scientific Officer for BrightFocus Foundation about the basic science and therapeutic research the Foundation is funding. Dr. Bovenkamp administers and ensures a high level of scientific accountability in the foundation's research grant award program and scientific review process, and serves as a scientific liaison, fostering strong relationships with grantees, the academic research community, and other like-minded non-profits.

Real World Health Care: It's estimated that there may be more than 14 million Americans with Alzheimer's disease by 2050. Why is the prevalence of this disease increasing?

Diane Bovenkamp: Part of it is demographics. The large, but aging Baby Boom generation is now entering the risk period for this disease. Each day, an estimated 10,000 Americans turn 65. And with today's longer life span, this population may be living with the disease for longer periods than in years past. Alzheimer's will take a growing toll on families, taxpayers, and the economy.

Another factor may be improved diagnosis of the disease. We can expect that as diagnostic tools get better—and there is less of a stigma surrounding the reporting of Alzheimer's as a cause of death—we will identify more people with the disease. These numbers may fluctuate, however. We may discover that some conditions that are currently being called Alzheimer's disease are actually other types of dementias that are new to us. In short, the way we look at or diagnose Alzheimer's may change.

RWHC: Where is most of the Alzheimer's disease treatment research being focused in this country: treatments to mitigate symptoms, treatments to cure the disease, to stop or slow the progression of the disease, or treatments to prevent the disease?

DB: Right now there are no drugs to stop Alzheimer's, only ones that mask symptoms, at best. Research is showing that there is no magic bullet or single pathway to attacking Alzheimer's. Our understanding of the disease is likely to come from multiple lines of inquiry. And we just don't have the time to limit the scope of inquiry.

There are a few trends, however, in the direction of new research. In recent years, BrightFocus has seen a dramatic shift towards prevention studies, or the examination of any activities, foods, or therapies that might reduce one's risk of the disease. For example, researchers are investigating the ties between reducing Alzheimer's risk by reducing one's risk of heart disease or diabetes. One could say that "what's good for the heart may be good for the brain."

Diagnosis or early detection is another area of study. Because disease symptoms may not appear until decades after the disease has begun, medical scientists have to find ways to detect and intervene early in the course of the disease—which at a minimum may slow or stop disease progression and its symptoms.

Advances in biomarkers, the indicators of a condition, have been huge in the last decade. Our design of clinical trials is evolving too. Cheaper, faster, and statistically rigorous designs are being used, and the use of repurposed drugs is also speeding up the discovery process.

RWHC: Where does BrightFocus Foundation concentrate its research funding?

DB: Our research support is investigator initiated, meaning that we don't dictate what topics to pursue, but offer our support—through a rigorous, peer-reviewed selection process—for any promising research idea from any investigator around the world. Our philosophy is that we will leave no stone unturned in the effort to end Alzheimer's disease.

BrightFocus is currently managing a portfolio of 74 Alzheimer's research projects around the globe and, since inception, we have funded more than $100 million in Alzheimer's research.

Our funded projects cover the usual range of topics including the roles of Amyloid Beta (ABeta), tau, and ApoE, as well as subjects like vascular factors, inflammation, cell death, bioenergetics, and neuroplasticity.

We encourage researchers to take risks that might not be funded elsewhere. We "bridge the gap," by supporting many scientists early in their career, who then go on to receive an average of ten times more funding from larger organizations such as the National Institutes of Health.

BrightFocus is known for its support of basic science, which is critical when we still have so much to learn about this disease. However, we have seen an increase in the study of potential therapies, with more translational (patient care) and clinical research projects each year. Drug discovery and diagnosis were two of the popular topics in our fiscal year 2016 grant awards, which will be announced later this summer.

You can read more about currently active research projects on our website.

RWHC: What are some of the most important Alzheimer's research breakthroughs that the BrightFocus Foundation has funded?

DB: We funded two researchers who went on to become Nobel Laureates. One is Stanley Prusiner, M.D., of the University of California at San Francisco (1997 Laureate) for research on how improperly folded protein can lead to disease, which has profoundly affected our knowledge of Alzheimer's. The other is Paul Greengard, Ph.D. (2000 Laureate), of the Rockefeller University. His research clarified the various parts of the signaling machinery in the brain and thus paved the way for the development of future therapies.

Other milestone achievements by scientists we funded include the initial identification and characterization of mutations in the familial (early-onset) type of Alzheimer's disease [amyloid precursor protein, presenilin 1 and presenilin 2 genes], and descriptions of the connections between the immune system and amyloid.

RWHC: What are some of the more promising Alzheimer's research programs you are currently funding?

DB: As I previously mentioned, BrightFocus has awarded more than $100 million to support promising research in fields ranging from molecular biology, genetics and drug discovery to clinical studies and epidemiology. We are currently supporting 74 outstanding Alzheimer's projects led by innovative researchers, so it's hard to highlight only a few of them.

Randall Bateman, M.D., at Washington University in St. Louis, is one of the original scientists to have developed a method called stable isotope labeling kinetics (SILK) to study the kinetics of proteins found in the human central nervous system. His SILK detection method for ABeta in the fluid surrounding the brain is currently the gold-standard for clinical studies. We are currently funding Dr. Bateman to develop a tau protein SILK detection method. ABeta and tau are two proteins involved in the progression of Alzheimer's. By measuring labeled tau, they will calculate how fast the brain produces tau and clears it away.

Recent news coverage has spotlighted the research of Donald Redelmeier, M.D., of the Sunnybrook Research Institute in Toronto. Leveraging Canadian health care records to examine a population of 300,000, he has been investigating whether use of statins reduces the long-term risk of dementia following a concussion. He is also looking at the connection between suicide risk and concussions, finding that a single mild concussion may triple the long-term risk of suicide.

And two of our funded researchers are looking at the linkage between Alzheimer's, body weight, and metabolism. Frank LaFerla, Ph.D., of UC-Irvine, is seeking to understand if the cognitive symptoms of Alzheimer's and Type 2 diabetes are linked. Makoto Ishii, MD, PhD, of Weill-Cornell Medical College in New York, is looking at why many Alzheimer's patients show early weight loss, and trying to understand how ABeta may interact with fat hormones. Success in these two studies could help scientists find early disease biomarkers.

RWHC: What do you see as the major obstacles or challenges facing Alzheimer's research today, and how is the BrightFocus Foundation helping to overcome these challenges?

DB: The biggest need at the moment is more funding for Alzheimer's research. We and others estimate that a minimum of $2 billion a year in research funding is needed if the U.S. is to reach the national goal of preventing and effectively treating Alzheimer's disease by the year 2025. Yet the US government spends far less. Not only are we losing the potential of new discoveries, but we are becoming increasingly ill-equipped to handle the needs of patients and families touched by Alzheimer's, along with other major health care costs.

That's one reason why BrightFocus and other members of advocacy coalitions are working together to educate policy makers that they can't afford to fund Alzheimer's research at inadequate levels. More and more families are becoming advocates for their loved ones with this disease. We provide advocacy suggestions and publications and other resources to spread awareness of the cost of Alzheimer's.

RWHC: Whether you are an Alzheimer's patient or a caregiver, living with this disease is difficult. Why is it so important for patients and their caregivers to have a support community? How is the BrightFocus Foundation helping to provide such a community?

DB: Alzheimer's disease takes a toll not only on the patient, but also on the health of loved ones and caregivers. Both patients and caregivers benefit from meeting with others who are going through the same experiences they are. They have lots of questions and issues to address. We provide a range of resources for families and individuals with the disease on questions to ask their doctor, financial and legal planning, housing concerns, and much more.

BrightFocus also joins forces with other advocates to increase public awareness and understanding of people with dementia. The new Dementia Friendly America initiative, which started in Minnesota, has as its mission to educate and mobilize communities across the US about the needs of people impacted by dementia.

We have also convened a panel of experts from Johns Hopkins, the University of Michigan, Indiana University, Purdue University Indianapolis, and the Veterans Administration to examine what it means to age at home. The objective of this Home-Based Dementia Care Panel is to raise awareness of home-based care in the context of a broader dementia care continuum, and to accelerate the development, testing, and dissemination of home-based dementia care interventions.

The panel is sparking discussion on closing the gap between patients and families in the health care system. The goal is to find out what allows people to "age in place with good quality of life and lower caregiver burden." Something most of us want in our own life.

To read this article on Real World Health Care, click here.

Alzheimer's Association Outlines Research Priorities & Treatment Horizons

This week, Real World Health Care brings you a conversation with Maria Carrillo, PhD, Alzheimer's Association Chief Scientific Officer. Formed in 1980, the Alzheimer's Association advances research to end Alzheimer's and dementia while enhancing care for those living with the disease.

Real World Health Care: According to your literature, more than 5 million Americans suffer from Alzheimer's disease. What do the majority of these patients most need in terms of treatments: treatments to address the symptoms of the disease, or treatments to stop or slow the progression of the disease? Why?

Maria Carillo: What people need most is hope – hope that comes from significant progress in Alzheimer's research that they can understand and that benefits their day to day life. Thanks to the amazing work of thousands of Alzheimer's Association advocates, and many dedicated legislators, we have in place a U.S. National Plan to Address Alzheimer's Disease. The Plan calls for real progress in treating and preventing Alzheimer's disease by 2025. An expert workgroup convened by the Alzheimer's Association recommended a federal investment of $2 billion per year for 10 years to make this achievement a real possibility. We are making strides toward that level of commitment – we're over half way there – but we still have a way to go.

To more directly answer your question, both symptomatic and preventive therapies have a lot of value. People with Alzheimer's, and those at high risk of getting it in the near-term, need something to help them now. Greatly reducing or eliminating dementia symptoms and/or pushing back the onset of dementia by ten, or even five, years, will act as something like prevention for the great majority of people – they will live most if not all of their lives free from debilitating symptoms.

Finally, we all look forward to the development of proven ways to reduce risk and prevent Alzheimer's disease and other dementias – for the millions of lives saved, the billions of dollars saved, and the enormous suffering eliminated.

RWHC: What are some of the most promising areas of treatment research that the Alzheimer's Association is funding?

MC: The Alzheimer's Association is the largest private, nonprofit funder of Alzheimer's research, awarding more than $350 million to more than 2,300 projects. Our goals are to (1) advance our

understanding of Alzheimer's, (2) help identify new treatments, (3) improve care, and (4) further our knowledge of brain health and Alzheimer's prevention.

The Alzheimer's Association has provided essential startup funding to, and/or funding to expand the scope of, three major Alzheimer's disease prevention trials currently underway – the A4 Trial, DIAN TU, and API APOE4.

The Alzheimer's Association grants program has funded – and continues to fund – some of the most important research threads in Alzheimer's science. These topics and ideas move the field forward by contributing to knowledge about Alzheimer's, refining research questions, and yielding clues to causes and treatments. Examples include:

- Sex, gender and vulnerability to Alzheimer's and other dementias
- Commonalities between cancer and Alzheimer's
- Effects of oxidative stress and inflammation in Alzheimer's
- Vascular contributions to Alzheimer's
- Protein misfolding and Alzheimer's
- Tau toxicity in Alzheimer's
- Biomarkers for Alzheimer's
- Development of new scales for Alzheimer's, including pain and clinical meaningfulness
- Vaccines/Immunotherapies for Alzheimer's
- Insulin and insulin-degrading enzyme in Alzheimer's
- Down syndrome and Alzheimer's
- Patient ability to consent in Alzheimer's
- Differences in Alzheimer's in minority communities
- Blood pressure control and Alzheimer's

RWHC: What are some of the biggest challenges or obstacles that Alzheimer's researchers are facing in terms of developing new treatments? What can or should be done to overcome those challenges or obstacles, and how is the Alzheimer's Association helping to overcome them?

MC: The two biggest issues/obstacles are insufficient funding for Alzheimer's research and the need for more participants for clinical studies.

The Alzheimer's Association and its nationwide constituency is the leading advocate for increased research funding at the federal level, and also the leading nonprofit funder of Alzheimer's research. That said, many more voices need to be heard – every day and through every vehicle – to ensure that the federal government understands exactly how high a priority this issue is, and allocates the needed funds.

Recruiting and retaining clinical trial participants is now the greatest obstacle, other than funding, to

developing new and better treatments for Alzheimer's disease. Before any drug or therapy can be used in medical practice, it must be rigorously tested to certify that it is safe and effective.

To address the growing need for clinical trial participants, the Alzheimer's Association launched Alzheimer's Association TrialMatch – a free clinical studies matching service. More than 100,000 individuals have registered to search for Alzheimer's clinical trials using TrialMatch.

Alzheimer's Association TrialMatch provides users with comprehensive clinical trial information and a customized list of studies they may seek to enroll in. TrialMatch is open to everyone, including people with Alzheimer's or other dementias, their caregivers, family members, and anyone who wants to get involved in the fight against Alzheimer's.

There are several other registries also working to identify and marshal individuals for Alzheimer's disease research. The primary need is for increased awareness that these services exist, and that participating in Alzheimer's research is one of the greatest gifts that one can give to current and future generations.

RWHC: Is a preventative or curative treatment on the horizon? Do you think this is a disease that can ultimately be prevented before it starts or cured after it starts?

MC: Similar to the way we address heart disease, the preferred strategy for Alzheimer's would include:

- Early detection methods that identify those most at risk. Preferably these would be simple, inexpensive and non-invasive, such as a blood test.
- Effective methods to track the biological course of the disease, and the impact of drugs and other interventions.
- Preventive and risk reduction strategies – lifestyle and pharmacological – that can be engaged in by everyone throughout life.
- Multiple effective treatments – that address the disease in multiple ways – for those who, despite the points above, suffer from dementia symptoms.

The Alzheimer's Association believes that all these things are possible in the relative near-term with the appropriate investment in research.

We have made great strides in treating and preventing many diseases – even major killers such as cancer, heart disease, and HIV/AIDS – when we have made the issue a high priority and made the resources available for research. Now is the time to do the same for Alzheimer's disease.

RWHC: What sort of initiatives or activities can we expect to see from the Alzheimer's Association over the next few years?

MC: We still do not completely understand the causes of Alzheimer's disease, and many questions

remain about exactly how it progresses. The Alzheimer's Association plans to redouble its efforts to support and spotlight in the basic science of the disease, for example at the Alzheimer's Association International Conference. Increasing our knowledge in these areas should uncover multiple opportunities for therapeutic targets.

At the same time, the Association is deeply involved in clinical trials aiming to prevent Alzheimer's disease. In addition to the funding initiatives mentioned earlier, we collaborate with Fidelity Biosciences Research Initiative (FBRI) and the principal investigators of all the major prevention studies in the Collaboration for Alzheimer's Prevention (CAP) seeking to facilitate the sharing of information, resources and expertise that may speed the discovery of new preventive treatments. CAP was first convened in 2011 to help researchers learn from and support each other's work; share data; harmonize data gathering and trial outcomes to allow for comparability across studies; and hold open, informal dialogue with regulators.

Inflammation is a factor that contributes to the cause and progression of many diseases and conditions. This is emerging as a significant area now in Alzheimer's research. The Alzheimer's Association's Part the Cloud initiative, for example, is making the development of new therapies in this area a target of multi-million dollars in research funding.

Newly launched is Alzheimer's Combination Therapy Opportunities (ACTO), which aims to provide pilot funding to explore combination therapy opportunities in Alzheimer's disease. This program will support a biomarker-based clinical trial testing of repurposed drug combinations through Phase II proof of concept.

The Alzheimer's Association also continues to prioritize issues such as the impact of sex/gender, race/ethnicity, education, and socioeconomic status on the development and progression of Alzheimer's and other dementias.

Read this story on Real World Health Care.

Patient Agitation in Alzheimer's Disease: Implications for Patients and Caregivers

Real World Health Care recently sat down with Anton Porsteinsson, MD, Department of Psychiatry, University of Rochester School of Medicine. Dr. Porsteinsson is the Director of the University of Rochester Alzheimer's Disease Care, Research and Education Program and has devoted his career to the care and study of individuals with memory disorders. Following up on his recent randomized clinical trial of citalopram, we discussed why it's important to focus on treatments for AD-related agitation — both for AD patients and their caregivers.

Real World Health Care: Why is it important to study agitation in patients with Alzheimer's disease?

Anton Porsteinsson: Agitation is quite common in people with AD. It has a huge impact on their quality of life, as well as their family members' and caregivers' quality of life.

RWHC: Prior to your CitAD Randomized Clinical Trial, why had previous pharmacological treatment options been deemed unsatisfactory?

AP: A number of medications have been studied over time for this condition, including atypical and conventional anti-psychotics and mood stabilizers. But the efficacy they showed, if any, was modest at best. At the same time, these medications have serious potential complications such as increases in cerebrovascular events, sedation, falls, Parkinsonism and even increased mortality.

RWHC: Your trial focused on patients receiving psychosocial intervention. Why is psychosocial intervention important for AD patients?

AP: Medications should rarely be the first line of treatment for AD patients. Not everyone needs to be treated with medications. That's why it's important to evaluate the root cause of the agitation problem. Is the patient agitated because of something going on in his or her environment? I remember a situation from a few years ago when I was seeing a summertime spike in agitation-related consultations from patients in a particular nursing home. It turns out the nursing home didn't have air conditioning. So it's not surprising patients were bothered and agitated. In AD cases, agitation may have as much to do with your roommate as your receptors.

Psychosocial intervention helps to channel nervous energy and restlessness by involving patients in something purposeful, or even giving them some sort of outlet, like an area to pace around where they are safe and not in anyone's way.

RWHC: The trial also focused on the effects of citalopram on caregiver distress. Why is this an important area of study?

AP: Caregivers, who are often family members with little or no medical training, may not understand what is going on with their loved one. They may take the patient's behavior personally, which can cause a great deal of stress. Even if you're a saint, it can build up and take a lot out of you.

Providing care for someone with AD is very hard under the best of circumstances. It's even more difficult when the patient is verbally or physically aggressive, uncooperative, or agitated. Caregivers need advice, support and tools to help them handle the situation. They need to learn to give themselves breaks, that it's OK not to be perfect, and that help is available for them. I find that a lot of caregiver stress is alleviated when, as health care providers, we listen to them and take their concerns seriously.

Caregivers need to know that agitation in AD patients is common and that there are ways to deal with it. Providers must connect them with resources like the Alzheimer's Association and community agencies. We need to help alleviate their concerns about finances. And we need to help them set up a working plan on how to deal with their situation — to bring order to the chaos.

RWHC: How will the results of the CitAD Randomized Clinical Trial inform your future AD research?

AP: This trial was extremely educational for the research community. It was one of the first studies to show that a medication was effective in multiple ways — both on a clinical scale in reducing agitation among patients and in reducing caregiver distress. We also found efficacy for other AD patient behaviors like anxiety, irritability and delusions or hallucinations.

On the flip side, we discovered some complications. Citalopram has been used widely for decades with vulnerable populations. But in the last five or six years, it's been found to not be as safe as once thought. It has the traditional SSRI side-effects of mild gastrointestinal distress and mild sleep pattern disturbances. But it also has been found to have an impact on cardiac conduction, especially in higher doses. In fact, when we were about three-quarters of the way through the study, the FDA suggested that, for people older than 60, there should be a dose limit of 20mg per day.

We confirmed this finding in our study. We also saw a drug placebo difference on a cognitive measure, the MMSE (Mini Mental State Examination). It isn't clear if this was due to baseline differences between the two groups and drift toward the mean, as the placebo group improved on the MMSE and the drug group saw a modest decline, or if it was a true modest cognitive toxicity. Until proven otherwise, we have opted to assume this is a potential side effect and we warn against it.

For our next study, we considered testing a lower dose of citalopram (20mg daily), but then we found that the active isomer of citalopram (S-citalopram) seemed to be better correlated to benefits seen in the study, while the inactive isomer (R-citalopram) more correlated with the adverse effects. S-citalopram is available as a generic drug, approved for depression and anxiety. We intend to study that drug further.

RWHC: What are some other areas of AD research you're currently involved in within the URMC Memory Care Program? What do you see as your most promising area of research?

AP: We have a broad portfolio of research programs at URMC. We're one of the more active academic-based clinical research programs in the country. Currently, we're conducting two behavior-focused studies. One is ongoing and is based on positive findings on dextromethorphan hydrobromide and quinidine sulfate, with a new formulation that uses less quinidine. We're also looking at methylphenidate for treatment of apathy in patients with AD.

We're also investigating new imaging techniques and various biomarkers to improve our ability to identify those at risk. And, we're working to find better ways of monitoring the progression of the disease and response to treatment through the ADNI study, which just received a fourth wave of funding.

Other areas we're investigating include prevention studies with people who are cognitively normal, but who have elevated beta-amyloid or genetic biosignatures that indicate future pre-disposition. We're looking at a passive and active vaccine against amyloid production. And we have a number of different studies on the prodromal stage of AD, working with beta secretase inhibitors that block the production of beta-amyloid.

It's actually a very exciting time in Alzheimer's disease research. We're seeing improved funding from federal sources and a rejuvenation of interest from the pharmaceutical industry. I'm quite optimistic that in the next five to ten years, we will make substantive progress in terms of our ability to limit AD. I think it's overly optimistic to expect a cure in that timeframe, but we can certainly make a dent, particularly from an early intervention standpoint. Treating this disease early is the critical factor.

Read this on Real World Health Care.

Dr. R. Scott Turner on Resveratrol and the Amyloid Hypothesis

This week, we sit down with R. Scott Turner, MD, PhD, Professor of Neurology at Georgetown University and Director of Georgetown's Memory Disorders Program. Dr. Turner specializes in cognitive behavioral neurology, memory disorders, Alzheimer's disease and Neurodegenerative dementias. Here, he discusses his latest research as well as the roles of resveratrol and anti-amyloid treatments in AD treatments.

Real World Health Care: Why is it so important in Alzheimer's disease treatment to find treatments that penetrate the blood-brain barrier?

Raymond Turner: Alzheimer's disease affects the brain, and only the brain. In order for a drug treatment to be effective, the drug must penetrate the blood-brain barrier to get into the brain. For example, a drug given orally will be absorbed into the blood, and a fraction of that drug will then penetrate the brain.

RWHC: Can you provide a brief overview of your current and near future research aimed at improving AD treatment options? What research program(s) are you most excited about?

RT: The leading treatment approaches in progress are focused on blocking amyloid production from amyloid precursor protein (APP). These are BACE-1 inhibitors given by mouth daily. Or, promoting amyloid clearance (anti-amyloid monoclonal antibodies given intravenously once a month). A small fraction of antibody gets into the brain to promote clearance.

Another approach includes development of more potent sirtuin activators (building on our resveratrol trial results). Finally, a class of drugs called tyrosine kinase inhibitors (repositioned cancer drugs) promote amyloid degradation in neurons in the brain by a process called autophagy.

A major new development in AD research has been the discovery of biomarkers, including amyloid PET and tau PET scans of the brain. With these new scans, we can see and quantitate AD pathologies before death instead of the classical approach of examining brain tissue under the microscope after death. This had led to treatment studies of earlier stages of AD called mild cognitive impairment (MCI) and prodromal AD. Treatment earlier in the disease process maybe more successful, and thus we are now moving towards AD prevention studies as well.

RWHC: Why study resveratrol in relation to AD?

RT: Major risk factors for AD include diabetes, midlife obesity, and metabolic syndrome. In contrast, caloric restriction (consuming two-thirds of normal daily calories) prevents all disease of aging in laboratory animals, including AD. It is not clear if this also applies to humans, but diabetes is known to accelerate aging in man.

How does calorie restriction prevent AD? We propose a link between energy metabolism and amyloid precursor protein (APP) metabolism, which is the normal turnover and breakdown of APP to amyloid. This link may be mediated by a group of proteins/enzymes/genes called sirtuins that link energy balance to gene expression. Resveratrol and other polyphenols directly activate sirtuins to mimic the effects of calorie restriction. While resveratrol may not be the optimal molecule due to its rapid metabolism and poor brain penetration, the effects of resveratrol in our trial point to a new pathway that may be exploited to develop more potent and patentable molecules (drugs) designed to prevent and treat AD.

RWHC: What, if anything, can be done to accelerate AD research?

RT: Given the financial cost of AD to society, AD is the most underfunded disease in the NIH portfolio. We desperately need more research funding to support parallel development of more preclinical and clinical research strategies. We also need more research volunteers. Currently, less than one percent of AD patients participates in research, partly because many are never diagnosed (dementia is not a diagnosis), and because many aren't aware of research opportunities. We also need more diverse participation in research. While our current study population is mostly Caucasian, AD affects the African-Americans and Hispanic population even more than Caucasians.

With greater funding and more research participation, we will develop safe and more effective strategies to prevent and treat AD. It's just a question of when.

RWHC: What is your position on treatments designed to target beta amyloid protein? There seems to be some debate within the research community.

RT: So far, we have not developed a new treatment for AD based on the amyloid hypothesis: that progressive amyloid deposition in the brain causes AD. While amyloid basically defines AD, many other important pathological processes are triggered by amyloid — inflammation, tau/tangle formation, neuronal loss, synapse loss and neurotransmitter loss. We think that anti-amyloid strategies now in the pipeline will be proven safe and effective for patients with AD. However, we will likely end up with a cocktail approach, similar to the management of diabetes, hypertension and HIV. This cocktail will likely include an anti-amyloid and an anti-tangle strategy.

RWHC: Why did you get into the field of AD research?

RT: As I was completing my neurology residency, transgenic mouse models of AD were just developed and published. This presented a great new opportunity to discover new treatments in mice, and then

translate these new treatments to the clinic with clinical trials. It turns out that the mice are easy to treat; we have over a thousand ways to cure AD in mice. But translation has not been so easy. We have not had a new FDA-approved drug for AD since 2003, but remain hopeful that strategies in the pipeline will be successful. All our research studies are add-on to the already available drug treatments for individuals with AD.

Read this story on Real World Health Care.

Attacking All Angles of Alzheimer's

By Emily Burke, Ph.D., Director of Curriculum Development, BiotechPrimer.com

Editor's Note: This article originally appeared in Biotech Primer Weekly. For more information on the science behind the headlines, please subscribe.

Alzheimer's disease ranks as one of the toughest nuts to crack within drug discovery and development. Current treatments merely manage symptoms, so finding a better solution becomes more and more urgent as the aging population grows.

The pathology most commonly associated with Alzheimer's disease (AD) is the buildup of amyloid-beta (Aß) plaques in the brain. Recent research from Stanford University suggests the plaques bind to a receptor on nerve cells, disrupting their function. However, there is no absolute consensus that these clumps of protein are the origins of AD or a symptom of the underlying cause.

Most experimental drugs have focused on "mopping up" or inhibiting the production of Aß plaques. Failures in early clinical trials dominate the treatment landscape, with a few potentials in the pipeline (aducanumab in Phase III). In the race to find a cure, every possibility offers a glimmer of hope, so let's shine a light on the developmental drugs stepping away from Aß plaques.

Loss of Neurons

A key clinical feature of AD patients is the loss of neurons. What if there was a therapy that could jump start the development of new neurons? Two companies are leading the charge in developing small molecule activators of neurogenesis. By screening large chemical libraries, they have identified various compounds that show promise in activating neurogenesis from adult neural stem cells, both in tissue culture and in mouse models.

In a mouse model of Alzheimer's, compound NNI-362 promoted the growth of new hippocampal neurons that not only migrated to the correct functional location but also differentiated and survived long enough to reduce the previously observed cognitive declines. The hippocampus is thought to play a role in memory formation and spatial navigation and is one of the first regions of the brain to show damage in AD. Phase I trials for NNI-362 are currently in preparation.

Another neurogenesis candidate, NSI-189, increased the hippocampal region of mouse brains by as

much as 20 percent. Phase I trials for NSI-189 were recently completed for major depressive order, with an aim to branch out to Alzheimer's disease in the future.

Engineering Yeast Cells

Rather than directly targeting Aß plaques, one group of researchers is working to identify their roots. By engineering yeast cells to produce the Aß protein, this research is monitoring the detrimental downstream effects of over-expression — like the disruption in the folding of other essential cellular proteins. Compounds that show promise in the yeast cells are then tested in AD patient-derived cells to screen for potential drugs. The sponsor is currently preparing to begin clinical trials with its lead compound.

Neuroinflammation

Another company is bypassing Aß plaques altogether and going after neuroinflammation. This pathway grew out of research conducted at Stanford, suggesting that a protein known as c1q is present in higher levels in the brains of AD sufferers. C1q accumulates at neuronal synapses, the key points of communication between brain cells. C1q also acts as a flag for other immune cells like macrophages — these "big eaters" chomp up cellular debris. The correlation of c1q could account for the observed reduction in synapse numbers and the accompanying loss of cognitive function seen in AD. The sponsor's lead candidate, now in preclinical development, is a monoclonal antibody which "mops up" excess c1q.

Proteasomes

A partnership between two sponsors is targeting AD-associated protein aggregates by activating a cellular component known as the proteasome. Proteasomes get rid of damaged proteins and dysfunctional protein aggregates by dismantling the peptide bonds holding them together. USP14 is one of the proteins that inhibits the proteasome, so this work is focused on the preclinical development of a USP14 inhibitor to allow proteasomes to be fully activated in AD patients.

Attacking Alzheimer's from all angles is the surefire way to get closer to better treatments and a real cure.

Read this article on Real World Health Care.