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Molecular Basis of Alzheimer's Disease: New Research Perspectives

By Rodrigo Morales, Ph.D. and Ruben Gomez-Gutierrez, M.Sc

Morales

Gomez-Gutierrez

Abstract: Alzheimer's disease (AD) is the most common type of dementia among people age 65 and over. The main pathological event associated with AD is the progressive accumulation into sticky plaques of abnormally folded proteins in the brain. It is widely accepted that a pathological form of the amyloid-β (Aβ) protein initiates the AD process. Thus, the focus in several research laboratories is to detect and disrupt misfolded protein aggregates. Here, we give an overview of our recent research (and that of others) revealing similarities between the behavior of the Aβ and the prion protein, which causes "mad cow" disease and Creutzfeldt-Jakob disease, a rare human brain disorder. We believe that an understanding of the similarities between these aberrant proteins can lead to the design of new diagnostic and therapeutic strategies for AD and other brain disorders.

Alzheimer's disease (AD) is the most common cause of dementia among people age 65 and over. In people younger than 60, the prevalence of AD is less than 1 percent. According to the Alzheimer's Association's 2018 report on the disease, the prevalence in the U.S. increases exponentially with aging: 32 percent of people older than 85 are affected by AD, and by age 90, the proportion rises to 63.9 percent. The Alzheimer's Association reports that about 5.7 million people suffer from AD in the United States, and the number is projected to reach 13.8 million by the year 2050. The aging of the population, due to rises in life expectancy, makes AD one of the most severe health problems in the U.S. and other developed countries.

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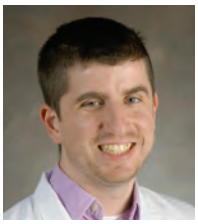
New Approaches to Treating Alzheimer's Disease at McGovern Medical School

By David H. Hunter, M.D. and Paul E. Schulz, M.D.



Hunter

Schulz

Abstract: Alzheimer's disease (AD), affecting 48 million people worldwide, is the most common neurodegenerative cause of memory loss. With the development of new imaging techniques, our ability to diagnose it has improved dramatically in the last few years. The new diagnostic tools have also unexpectedly taught us that the processes underlying AD begin decades before the first symptom appears. There is currently no disease-modifying treatment for Alzheimer's, but these significant breakthroughs in understanding the disease's underlying processes have led to the rational development of unique new types of medications. Here at UTHealth, basic scientists and clinicians work together and with others around the world to advance and test new treatments for this very distressing disorder. It is our hope that important new treatments will emerge in the not too distant future.

At McGovern Medical School's Memory Disorders and Dementia Clinic, we see patients with changes in their memory, thinking, emotions, and behavior. The most common cause of memory loss is Alzheimer disease (AD), but there are many other disorders that affect memory or cause dementia, including Parkinson's disease, Lewy body dementia, frontotemporal dementia, Huntington's disease, and vascular dementia. Dementia-like syndromes may also be caused by depression, sleep apnea, medications, and other medical illnesses. To determine the cause of a person's symptoms, a thorough

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Director's Column

From the Director, John H. Byrne, Ph.D.

Of all the diseases humans may fall prey to, I think the one that concerns people most is Alzheimer's. It affected 5.5 million Americans (age 65 and older) in 2018, according to the Alzheimer's Association, and is projected to affect 7.1 million, age 65 and older by 2025. That's a 29 percent increase within a 7-year period, with the cost to society already running in the hundreds of billions of dollars annually. The search for new effective treatments and a cure is widespread and intense. This issue of the NRC Newsletter spotlights the work of two UTHealth faculty dedicated to the development of treatments for this horrible disease and its eradication.

Rodrigo Morales, Ph.D., associate professor of neurology in McGovern Medical School's George and Cynthia Mitchell Center for Alzheimer's Disease and Related Brain Disorders, and his co-author, Ruben Gomez-Gutierrez, M.Sc., a doctoral candidate at the University of Malaga in Spain, provide a quick overview of the disease and some of the main ideas about its molecular causes, particularly the misfolding of the amyloid beta protein. They also discuss their current research; it focuses on similarities in the behaviors of amyloid beta and the prion protein, which is the causal agent of other neurodegenerative diseases, including "mad cow" disease and, in humans, Creutzfeldt-Jakob disease. The newsletter's companion article is by Paul H. Schulz, M.D., the Rick McCord Professor in Neurology at McGovern Medical School and director of the Memory Disorders and Dementia Clinic, and David H. Hunter, M.D., assistant professor of neurology at McGovern Medical School's Neurocognitive Disorders Center. Dr. Schulz works with scientists in the Mitchell Center, particularly its director, Claudio Soto, Ph.D., professor and holder of the Huffington Foundation Distinguished Chair in Neurology, to translate research into treatment through the clinical trials he oversees. I hope the dedication of these authors offers inspiration to those readers whose lives may be personally touched by Alzheimer's.

Our friend and neuroscience colleague, Eric Kandel, whose latest book, *The Disordered Mind*, came out just last August, has—with characteristic delight—previously described biologists as "delusional optimists." We tend to believe there is no mountain we cannot scale. Although the brain is a vast frontier, we can discover the answers to all our questions. It is only a matter of time and funding for research. I share his perspective.

Here at UTHealth, we have solid reason for such optimism, especially with regard to better care for people with major mental illnesses. Construction of an innovative psychiatric hospital will begin this summer on land adjacent to the existing UTHealth Harris County Psychiatric Center (HCPC). The new facility, together with HCPC, will comprise the UTHealth Continuum of Care Campus for Behavioral Health. Created with $125 million in state funds, the new hospital and campus, to be managed and staffed by the Department of Psychiatry and Behavioral Sciences at McGovern Medical School, with department chairman Jair Soares, M.D., Ph.D. as executive director, will provide our region with an additional 240 beds. The first public mental health hospital built in Houston in more than 30 years, it will be the largest academic psychiatric hospital in the country. It will have a strong focus on patient care with a design that strategically incorporates natural light, access to the outdoors, uncrowded space, and acoustics to encourage healing. In addition, it will include space for research and education. The campus will serve as a continuum of care model for the country and will be a step towards the improvement of the whole system of care in Texas.

Psychiatry is in a golden age of research. Previous distinctions between neurologic and psychiatric disorders are increasingly blurred with new discoveries about the biological bases of mental disorders that in the past were considered, for example, to be the result of bad parenting. Such recent research discoveries provide additional grounds for optimism in neuroscience and the development of new treatments for people suffering from a range of serious mental and behavioral disorders. The promising outlook in psychiatric research was implicit in the NRC's 2018 neurobiology of disease course. This year the course was on the leading-edge field of epigenetics of brain disorders.

Serving with me as course co-director was Consuelo Walss-Bass, Ph.D., associate professor and director of the UTHealth Psychiatric Genetics Program in the Department of Psychiatric and Behavioral Medicine. She wrote about her findings on the genetic underpinnings of schizophrenia in the NRC Newsletter's spring 2017 issue. Recently, she and her colleagues, including among others, Dr. Soares and instructor, Gabriel Fries, Ph.D., published the group's interesting findings of their epigenetic research on youth at risk for bipolar disorder (BD) (Fries et al 2017). In addition to their identification of 43 risk genes for BD, they found that in families with parents who have BD, stress in the home environment can affect the offspring's epigenetic profile and contribute to the manifestation of the disorder. As the authors note, this was a preliminary study with a small sample and requires replication in a larger cohort, but it serves to illustrate what I mean by psychiatric research in a golden age.

Dr. Walss-Bass designed our epigenetics course to include a broad array of subjects and lecturers from throughout UTHealth, The UT MD Anderson Cancer Center, and Baylor College of Medicine. The presentations overall had encouraging implications for the development of new knowledge about environmental interactions with genes. For example, Dr. Fries noted that epigenetic research will bring important discoveries about the biomedical roles of those factors on the development of such pathologies as posttraumatic stress disorder and substance abuse, to name just two. He also suggested that as a result of epigenetic research and the related burgeoning of personalized psychiatry, new approaches for reversing environmental effects may soon emerge. Clearly, such epigenetic studies as those

Continued from page 2; Byrne

on BD currently underway in the Department of Psychiatry and Behavioral Sciences would integrate in ideal ways with the UTHealth Continuum of Care Campus, where clinicians attuned to the value of biomedical research could quickly use the findings for treatment of their patients.

In closing and re-focusing on the neurobiology of disease/epigenetics course, I want to highlight the educational component of the NRC's mission as a top priority. That holds true for students of any age, from young children all the way through medical and graduate school. Although the neurobiology of disease course is primarily for UTHealth graduate students (and also attracts a sprinkling of faculty and postdoctoral fellows), the class is a requirement for a select group of second-year medical students—those who are in our "Scholarly Concentration in the Neurosciences" enrichment program. Co-directed by me and Ian Butler, M.D., professor in the departments of pediatrics and neurology, the neuroscience concentration program is one of 11 offered in McGovern Medical School. Each student in the program works with his or her faculty mentor to design and conduct a neuroscience research project, whether laboratory-based or clinical in nature. The research project then serves as a springboard for their participation in the related scholarly activities of writing, publishing, and speaking about their research or conducting additional studies. Watching the academic talents of these students develop and bloom over the course of their medical training is surely another reason for optimism.

From left to right, John Byrne, Ph.D., co-director of the NRC's neurobiology of disease course; Melanie Carless, Ph.D., associate professor of genetics at the Texas Biomedical Research Institute in San Antonio, Texas and course guest speaker, Sept. 24, 2018; Consuelo Walss-Bass, Ph.D., associate professor, Dept. of Psychiatry and Behavioral Sciences at McGovern Medical School, and co-director of the course.

McGovern Medical School students in the Scholarly Concentration in the Neurosciences program attend the neurobiology of disease course in the fall of their second year, after completing their summer research project, a cornerstone of the program. From left to right are students Albert Amran and Panayotis Apokremiotis with Dr. Melanie Carless; Ana Maria Dragan, medical student; and Dr. Consuelo Walss-Bass.

Valentin Dragoi, Ph.D., holder of the Rochelle and Max Levit Distinguished Professorship in the Neurosciences at McGovern Medical School, received a grant from the NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. This is his third award from the highly competitive BRAIN Initiative. The project's multiple PIs include **Anthony Wright, Ph.D.,** professor of neurobiology and anatomy at McGovern Medical School, and Rice University professor of electrical and computer engineering, Behnaam Aazhang, Ph.D. The team is focusing on areas of the brain responsible for vision and executive control and the involvement of these areas in social interactions. The research will potentially lead to new understanding of complex network computations in normal and dysfunctional brain states, including autism.

Georgene W. Hergenroeder, Ph.D., assistant professor in the Vivian L. Smith Department of Neurosurgery at McGovern Medical School, has received a grant for neurotrauma research from Mission Connect, a collaborative funding program of the TIRR Foundation. Her research aims to determine whether there is a causal relationship between neuropathic pain in patients with spinal cord tissue pathology and the presence of autoantibodies to GFAP (glial fibrillary acidic protein), found in astrocytes.

Cameron Jeter, Ph.D., associate professor in the UTHealth School of Dentistry Department of Diagnostic and Biomedical Sciences, has received a grant from the Parkinson's Foundation to identify the oral bacteria in patients who have had Parkinson's disease for 10 years or longer. Such patients develop difficulty swallowing, putting them at increased risk of aspiration pneumonia, the primary cause of death in patients with Parkinson's.

Hyun-Eui Kim, Ph.D., joined the McGovern Medical School Department of Integrative Biology and Pharmacology as assistant professor. A recipient of a University of Texas System Rising STARs (Faculty Science and Technology Acquisition and Retention) award, she is developing a research program based on discoveries as a postdoctoral fellow at the University of California, Berkeley, related to the role of mitochondrial stress responses on age-related protein misfolding diseases, such as Alzheimer's, Parkinson's, and Huntington's.

Louise McCullough, M.D., Ph.D., professor, Roy M. and Phyllis Gough Huffington Distinguished Chair, and chair of the McGovern Medical School Department of Neurology, and **Fudong Liu, M.D.,** assistant professor of neurology and director of translational stroke research, are multiple PIs on a new NIH/NINDS grant to examine the effects of the X chromosome and its genes on stroke in aged animals of both sexes. They will also explore the underlying mechanisms in stroke, with a focus on the interaction between sex and the immune responses. A member of Dr. McCullough's BRAINS research lab, Yun-Ju Lai, M.S., has received a predoctoral fellowship from the American Heart Association to examine the effects of aging and stroke on programmed death-ligand 1 expression.

Fabricio H. Do Monte, D.V.M., Ph.D., assistant professor of neurobiology and anatomy at McGovern Medical School, has received a Young Investigator grant from the Brain and Behavior Research Foundation to investigate the association in rats between fear disorders and eating disorders such as anorexia, bulimia, and obesity. His research will focus on the paraventricular nucleus of the thalamus, a region known to be interconnected with areas of the brain implicated in the control of food-seeking and fear response.

Ines Moreno-Gonzalez, Ph.D., assistant professor of neurology at McGovern Medical School, received a New Investigator grant from the Brain and Behavior Research Foundation to study whether late-life depression can trigger the onset of Alzheimer's disease and accelerate its progression. She also received a grant from the Texas Alzheimer's Research and Care Consortium to develop a new approach that uses a stem cell-based non-invasive therapy for treating Alzheimer's.

Sandra Pritzkow, Ph.D., assistant professor of neurology at McGovern Medical School, received a grant from the Texas Alzheimer's Research and Care Consortium to develop a diagnostic blood test for Alzheimer's disease. She also received a grant from the Michael J. Fox Foundation for Parkinson's Disease. Her project is on the detection of alpha-synuclein aggregates, a biomarker for Parkinson's, in cerebrospinal fluid.

Christophe P. Ribelayga, Ph.D., associate professor in the McGovern Medical School Ruiz Department of Ophthalmology and Visual Science, is a multiple PI with **Stephen C. Massey, Ph.D.**, professor, holder of the Elizabeth Morford Chair in Ophthalmology, and research director for the department, on an NIH/NEI grant to study the function of rod/cone gap junctions in retinal circuitry. They also received a supplement grant to purchase a 2-photon microscope and ancillary equipment for the retinal research. In addition, Dr. Ribelayga is a multiple PI with **Jiaqian Wu, Ph.D.**, associate professor in the McGovern Medical School Department of Neurosurgery and the Institute of Molecular Medicine's Center for Stem Cell and Regenerative Medicine, on an NIH/NEI grant. They are investigating the role of circadian clocks in the development, maintenance, and function of the various types of photoreceptors in the mouse retina.

Mohammad Shahnawaz, Ph.D., assistant professor of neurology at McGovern Medical School, has received a grant from the Michael J. Fox Foundation for Parkinson's Disease. His project is

the detection of alpha-synuclein aggregates in the cerebrospinal fluid of people carrying an LRRK2 genetic mutation.

Rachael W. Sirianni, Ph.D. was named a UT System Rising STAR and joined McGovern Medical School last fall as assistant professor in the Vivian L. Smith Department of Neurosurgery. Trained as a biomedical engineer in polymeric drug delivery, she has designed creative approaches for treating central nervous system disease via encapsulation and tissue-specific delivery of drugs from polymeric nano-particles. Her goal at UTHealth is to develop nano-particle systems that can treat central nervous system infiltration and metastasis in children affected by recurrent malignant brain tumors.

Jair C. Soares, M.D., Ph.D., professor, chair of the McGovern Medical School Department of Psychiatry and Behavioral Sciences, and holder of the Pat R. Rutherford, Jr. Chair in Psychiatry, was named president of the International Society for Affective Disorders.

Claudio Soto, Ph.D., professor of neurology, Huffington Foundation Distinguished Chair in Neurology, and director of The George and Cynthia Mitchell Center for Research in Alzheimer's Disease and Brain Related Disorders at McGovern Medical School, recently received several new grants. As multiple PIs, he and **Rodrigo Morales, Ph.D.,** associate professor of neurology at the Mitchell Center, received an NIH/NIA grant to isolate and characterize different amyloid-beta conformational strains from the brains of patients with Alzheimer's disease and animal models. In addition, Dr. Soto and **Roberto C. Arduino, M.D.,** professor of infectious disease in the McGovern Medical School Department of Internal Medicine, are multiple PIs on a new NIH/NIA grant to study misfolded protein aggregates in the brain and biological fluids of HIV-infected people. Dr. Soto is also a multiple PI on another NIH/NIA grant with **Eva Sevick-Muraca, Ph.D.,** professor and director of the Center for Molecular Imaging at the McGovern Medical School's Brown Foundation Institute of Molecular Medicine. Their project is to study age-related lymphatic dysfunction on the pathogenesis of Alzheimer's disease. As a leading, senior scientist in Alzheimer's research, Dr. Soto recently was named winner of the prestigious Zenith Fellows research award from the Alzheimer's Association. His project is to develop a "mini-brain" from cells of people who had the disease and to study the molecular basis of the disease, as well as the use of compounds for treating it. In addition, Dr. Soto has received a grant from the ALS Association for his project, "Development of a biochemical diagnosis for ALS by high-sensitive detection of misfolded protein oligomers in biological fluids."

Consuelo Walss-Bass, Ph.D., associate professor of psychiatry and behavioral sciences at McGovern Medical School, and **Joy M. Schmitz, Ph.D.,** the Louis A. Faillace, M.D. professor of psychiatry and behavioral sciences, have received a supplement grant from the NIH/NIDA for a new project investigating DNA methylation in the postmortem brains of people with addiction. They are multiple PIs, together with Rodrigo Grassi-Oliveira, Ph.D., of the Pontificia Universidade Catolica in Rio Grande do Sul, Brazil.

In Other News…

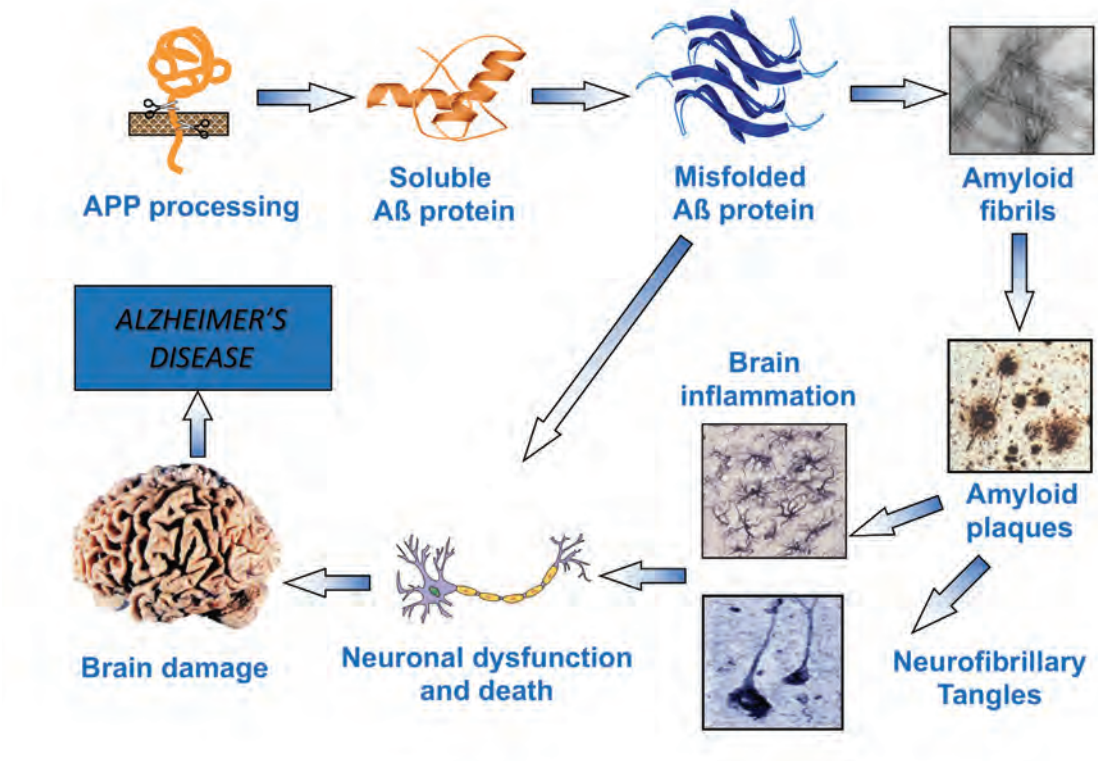
Samantha Debes, Ph.D. student in the MD Anderson UTHealth Graduate School of Biomedical Sciences, is the first recipient of the Terry J. Crow, Ph.D. Scholarship in Neuroscience, created in the Dept. of Neurobiology & Anatomy at McGovern Medical School. Pramod Dash, Ph.D., professor and interim chairman of the department, presented her with the award certificate at the Neuroscience Program student retreat held in Galveston, Texas at the San Luis Resort and Conference Center Sept. 7, 2018.

The disease was formally introduced by the German neuropathologist Alois Alzheimer, who in 1906 first described the typical dementia-associated clinical signs, characterized by extensive and progressive loss of memory. These symptoms were associated with unique pathological changes in the brain, including the abnormal accumulation of protein deposits in specific brain regions, such as the hippocampus, the entorhinal cortex, the amygdala, and the basal ganglia. The clinical course of AD lasts an average of eight to 10 years, but some cases have been reported to reach 25 years. In the terminal phase, patients die due to secondary causes, pneumonia being the most common.

A small proportion of AD cases (less than 5 percent) are due to genetic mutations. The large majority arise sporadically, meaning that the disease is triggered by one or more factors unlinked to any known specific event or cause. Although the particular triggers leading to AD have not been fully characterized, risk factors have been identified. These include aging, sex, ethnic groups, smoking, high-fat diet, and sedentary lifestyle, among many others. In addition, pathological conditions such as diabetes, hypertension, and cerebrovascular accidents are associated with increased risk for developing AD. At present, there is no cure for AD; treatments are palliative and only effective for early symptoms.

Fortunately, not everything related to AD is bleak. Since its first description, researchers have elucidated several aspects of the disease's progression. At the molecular level, the predominant framework for research in AD is the amyloid cascade hypothesis, postulated by Hardy and Higgins in 1992. The basic idea is that amyloid beta (Aβ), a proteolytic product of the larger transmembrane amyloid precursor protein (APP), misfolds and accumulates, leading to the formation of the sticky plaques outside the cells that are typically found in the brains of AD patients. (See Figure 1.) The abnormal accumulation of Aβ peptides, due to an altered balance between the biogenesis and clearance of Aβ in the brain and to the peptide's aberrant folding, leads in turn to a chronic inflammatory response (as shown by the activation of microglial and astroglial cells) and to the abnormal hyperphosphorylation of the tau protein. The hyperphosphorylated tau protein then forms the aberrant neurofibrillary tangles inside neurons that are also indicative of AD. Other key events in the amyloid cascade are the disruption of axonal transport, emergence of dystrophic neurites, synaptic loss, and neuronal death. All these pathological events contribute to progressive cognitive decline.

Figure 1. Amyloid-β (Aβ) in Alzheimer's Disease



Aβ is a proteolytic product of the transmembrane amyloid precursor protein (APP). It is generated as a normal physiological product, but under certain circumstances, the protein misfolds and aggregates in fibrillary structures. These amyloid fibrils later accumulate in the brain to form amyloid plaques. Different misfolded Aβ aggregates (oligomers, protofibrils, and fibrils) are toxic to neurons and also trigger other pathological events (glial activation, tau hyperphosphorilation, etc.) that further contribute to neuronal dysfunction and typical clinical symptoms of the disease.

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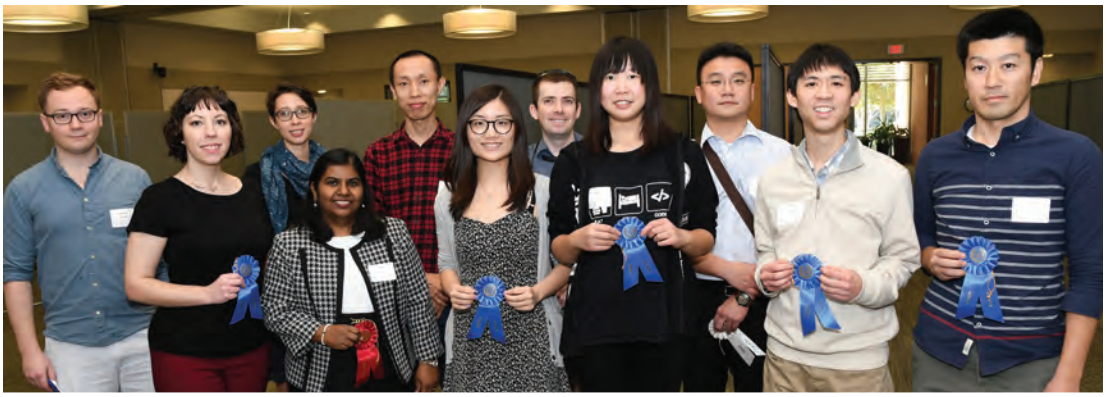
In*the*Spotlight



Left: *Winners of the NRC's 25th Annual Neuroscience Poster Competition, Dec. 2018, included students and postdoctoral fellows from Baylor College of Medicine, Rice University, and UTHealth.*

Right: *UTHealth faculty, students, post-docs, and other colleagues gathered at the NRC reception at the Society for Neuroscience Conference, Nov. 3-7, 2018, in San Diego, Calif.*

Left: *Left to right, from UTHealth are Elsa Rodarte, M.D., resident in neurology, with others in the dept. of neurobiology & anatomy, Natasha Kharas, M.D./Ph.D. candidate; Roger Janz, Ph.D., associate professor; Ariana Andrei, Ph.D., postdoctoral fellow; Valentin Dragoi, professor; and Fabricio Do Monte, assistant professor.*

Right: *From left are Carmen Canavier, Ph.D., professor, Louisiana State University Health Sciences Center (LSUHSC); Elyssa Margolis, Ph.D., associate professor, UC San Francisco; and Sonia Gasparini, Ph.D., associate professor, LSUHSC.*

Left: *Left to right are Evangelos Antzoulatos, Ph.D., scientist, UC Davis; Jose A. Fernandez Leon Fellenz, D. Phil., Ph.D., UTHealth postdoctoral associate; Yue Yu, UTHealth doctoral candidate; Renan Costa, UTHealth doctoral candidate; Riccardo Mozzachiodi, Ph.D., associate professor, Texas A&M University-Corpus Christi; and Abraham Susswein, Ph.D., professor, Bar-Ilan University.*

interview, neuropsychological testing, and sophisticated imaging tools are used. Having determined the diagnosis, our goal is to provide the best treatment possible.

Alzheimer's disease is the only neurodegenerative disease with FDA-approved treatments: Two classes of oral drugs help the symptoms of AD; however, they do not stop or reverse the disease. The need for real disease-modifying treatments is truly urgent since 48 million people worldwide already suffer from it and many others are at risk. We at the Department of Neurology's Memory Disorders and Dementia Clinic are fortunate to work with the basic scientists in the UTHealth Mitchell Center for Alzheimer's Disease and Other Brain Related Illnesses to translate cutting-edge laboratory discoveries into treatments for our patients. They include Dr. Rodrigo Morales, who describes his recent research with Ruben Gomez-Gutierrez related to AD in the companion article in this newsletter, as well as his colleagues, including Claudio Soto, Ph.D., professor of neurology and director of the Mitchell Center.

Thirty years ago, the scientific community knew from microscopic examination of tissue that Alzheimer's dementia is associated with amyloid plaques and neurofibrillary tangles, but we had no idea what the plaques or tangles contained. After years of study, it is now known that plaques and tangles are composed of amyloid beta (Aβ) and tau proteins, respectively, which are thought to be causative. That insight has led to promising new treatment trials directed at these proteins.

The amyloid precursor protein (APP) is a normal protein in neurons; it is thought to be involved in cell signaling. A small extracellular fragment of APP is normally cleaved by the enzyme alpha-secretase, but on rare occasions, APP is instead cleaved by both beta- and gamma-secretase. The abnormal fragment that results is called Aβ, an extremely sticky peptide that tends to attach to itself and form plaques. All humans produce Aβ throughout their lives. Some are naturally able to clear the compound from the brain before it has a chance to coalesce, but for others, the plaques grow large enough that they become insoluble and trapped in the brain. It is believed that this sets off a cascade of events that eventually leads to brain cell death and the symptoms of AD.

Historically, amyloid could only be identified in postmortem histology. Now, our diagnoses during life are much more accurate due to the development of a special PET scan that directly visualizes amyloid plaques in the brain. In addition, cerebrospinal fluid assays are available to measure the Aβ to tau ratio, which is also diagnostic. In current drug research, all prospective patients with the symptoms of AD are tested to be sure that amyloid is present before we start treatment, as several unrelated pathologies can mimic AD clinically. While these tools were developed to diagnose AD, their use has now revealed the very surprising finding that the accumulation of amyloid plaques can precede cognitive symptoms of AD by up to 20 years. Since this accumulation is the first identifiable pathology in AD, the prevailing, but not universally agreed upon belief among researchers, is that amyloid is the ultimate initiator of the disease, which is known as the amyloid hypothesis.

Two major strategies are currently used to target amyloid: removing the amyloid that is already present and stopping more amyloid from being produced. To potentially remove the amyloid already present, we are employing anti-amyloid antibodies that harness the patient's immune

Dr. Schulz uses images from PET scans, MRIs, data from neuropsychological tests, interviews, and other diagnostic tools, together with a model of the brain to explain his assessment regarding a patient's memory disorder.

Claudio Soto, Ph.D., professor of neurology and director of The George and Cynthia Mitchell Center for Research in Alzheimer's Disease and Brain Related Disorders at McGovern Medical School, (left) and Dr. Schulz confer at their recent monthly meeting about new lab results and possibilities for their translation to human clinical trials.

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system. When the antibodies attach to amyloid, the white blood cells of the brain appear to recognize the amyloid as foreign and phagocytize it. A variety of antibodies have been developed, differing in their abilities to cross the blood brain barrier, their affinities for amyloid plaques versus soluble amyloid, and their methods of administration. Here at UTHealth Neurology, we collaborate with others in large multicenter trials to test such antibodies in patients with early symptoms of AD. Patients receive monthly intravenous or intramuscular injections of antibodies, with the hope of reducing plaque burden and improving clinical outcomes. Early trials have demonstrated safety and shown that these drugs are efficient at removing amyloid from the brain. Only with large Phase III trials, however, can we test whether the drug will improve cognitive outcomes.

The second approach targeting amyloid is to prevent Aβ from being produced. As noted, the enzymes beta- and gamma-secretase are required to act on APP in order for the sticky Aβ to arise, so downregulating these enzymes is an obvious drug target. Gamma-secretase was targeted first, but it proved to be vital to other brain signaling pathways and its inhibitors were associated with limiting side effects. Most beta-secretase (BASE) inhibitors, however, appear to be safe in both animal and early human trials and have proven to reduce new amyloid production by around 90 percent. Several BASE inhibitors that are chemically unrelated have been developed, and some of them have already undergone Phase III trials. Although halting the production of new amyloid does not seem to have a positive impact on cognition in patients with well-established symptoms of AD, there is hope that patients with milder symptoms may show benefits from this class of medications. Most importantly, it may be that persons with amyloid deposition and no symptoms are most likely to benefit from this class of medications. For this reason, we are currently involved in trials of BACE inhibitors at this presymptomatic phase of AD. We are targeting persons age 60 to75 who have a risk for amyloid deposition and who might participate in long-term trials with the goal of reducing amyloid production. We are very hopeful that this type of approach may someday prevent the development of AD.

While we are testing treatments that rely on the amyloid hypothesis, there is a second protein whose deposition appears to more closely correlate with symptoms—that is, tau protein, which forms intraneuronal neurofibrillary tangles. These tangles may exert a greater direct effect on neuronal cell death. As a result, a major new initiative in AD treatment trials is to attempt to reduce tau protein in the brain to test the impact on symptom development. Along these lines, we are initiating a trial of multiple anti-tau antibodies, as each one targets different forms of the tau protein, in very early AD. Patients will receive monthly intravenous infusions in our clinic's state-of-the-art infusion center.

The tau protein is also pathologic in several non-Alzheimer forms of dementia, where it occurs in the absence of amyloid. One example is progressive supranuclear palsy (PSP) and others are forms of frontotemporal dementia (FTD). We have been giving tau antibodies to PSP patients for the last year and hope to test them in FTD patients at some point.

In AD, the third component of cell death appears to be inflammation. Thus, we have a single-site trial targeting amyloid, tau, and inflammation.

Alzheimer's disease continues to be a devastating illness with few available therapies, but we as a scientific community have come a long way in the last few decades. Though AD research can be frustrating, at long last we understand enough of the biology underlying the disease to develop rational therapies. We are grateful to our basic science colleagues who help generate new treatment ideas and especially to our patients who volunteer their time and effort to enroll in clinical trials. With the participation of all, we are confident that we can eventually bring an end to this awful disease.

About the Authors

David H. Hunter, M.D. is an assistant professor of neurology at the UTHealth McGovern Medical School's Neurocognitive Disorders Center. In addition to evaluating patients with memory disorders, Dr. Hunter participates in clinical trials, teaches at the Neurology Residents' Continuity Clinic, and serves as the cognitive specialist at the UTHealth Huntington Disease Center of Excellence. After receiving his B.S. in biomedical engineering at The University of Texas at Austin, he completed medical school, neurology residency, and a neuropsychiatry fellowship at UTHealth.

Paul E. Schulz, M.D. is the UTHealth McGovern Medical School Rick McCord Professor in Neurology, director of the Memory Disorders and Dementia Clinic, and director of the Neuropsychiatry and Behavioral Neurology Fellowship. He completed a combined B.A.-M.D. degree program at Boston University and an internship in internal medicine, followed by a residency in neurology and a fellowship in cellular neurophysiology at Baylor College of Medicine. He stayed at Baylor as faculty and directed a basic science laboratory for 20 years examining the cellular mechanisms underlying learning and memory. At the same time, he developed a neuropsychiatry practice and obtained subspecialty certification in behavioral neurology and neuropsychiatry by the UCNS. Currently at UTHealth, Dr. Schulz researches better diagnostic tools for Alzheimer's disease, illuminates risk factors for it, and directs numerous treatment trials for Alzheimer's and other neurodegenerative diseases.

Any point along the amyloid cascade is a potential target for research that might lead to the development of diagnostic tools and treatments. Various alternative hypotheses guide the work of some investigators. For example, proponents of the tau hypothesis believe that hyper-phosphorylated tau aggregation is the causative agent of the disease. Other researchers believe the cause is related to inflammatory processes, oxidative stress, vascular impairments, cholesterol, or metal accumulation in the brain.

However, the large majority of current research strategies target the misfolding of Aβ. Our laboratory in the Mitchell Center for Alzheimer's Disease and Related Brain Disorders at McGovern Medical School at UTHealth is specifically interested in studying how Aβ misfolds, aggregates, and spreads in the brain. Our mechanistic studies take into consideration lessons obtained from another protein of similar behavior: the prion. The prion protein is responsible for transmissible spongiform encephalopathies (e.g., "mad cow" disease) and may act as an uncommon infectious agent. Due to the leading role of protein aggregates in AD and the shared structural and biochemical features of prions and Aβ, we are studying similarities in the behaviors of these disease-associated proteins in the brain. To our surprise, we have observed that they behave similarly both in vitro and in animal models, particularly in their spreading mechanisms.

Because of the infectious nature of the prion, comparisons between it and Aβ have caused controversy in the field. However, with funding awarded by the Alzheimer's Association and The National Institute of Aging in support of our research direction, our findings may lead to a significantly better understanding of AD and to the development of new treatments. We have seen that the injection of patient-derived Aβ aggregates into transgenic mice can accelerate pathological outcomes (Morales, Bravo-Alegria, et al. 2015. Scientific Reports) and even generate pathology in animals that would otherwise not occur (Morales et al. 2012. Molecular Psychiatry). The extent of induced pathological changes depends, just as with prions, on the amount of Aβ aggregates administered into experimental subjects (Morales, Bravo-Alegria, et al. 2015. Scientific Reports). We also have observed that the injection of brain samples from pre-symptomatic cases of AD can "transmit" pathology to experimental mice (Duran-Aniotz, et al. 2014. PLOS One) and that transmission can be prevented by removing pathological Aβ from the samples (Duran-Aniotz et al. 2013. Acta Neuropathologica Communications). Recent studies conducted by several researchers (mostly in Europe) have shown that some patients receiving (intramuscular) human-derived growth hormone preparations developed unusual early-onset Aβ pathology in their brains. Similar events were observed in cases of Creutzfeldt-Jakob disease, a rare, fatal brain disorder (a type of prion disease in humans). As described mostly in the 1980s, the pathology was transmitted through certain medical procedures, including the administration of cadaveric growth hormone retrieved from prion-diseased individuals. Fortunately, no confirmed transmissible cases of AD have ever been reported, and current evidence in animal models and human samples suggests that if these events were to ever happen, they would occur only under extreme and rare circumstances.

Considering the prion-like behavior of Aβ, we are also studying the possible variation in its morphology/conformation and the consequences of this in disease. Our idea is that different structural morphologies or "strains" of Aβ may exist in the brains of AD patients. Different proportions of these diverse strains may be responsible for the varied clinical manifestations observed among affected individuals. Our preliminary data show that different populations of Aβ structures may generate detrimentally different pathological outcomes in laboratory animals, as similarly observed in prion diseases.

We strongly believe that understanding the shared behaviors of pathological Aβ and infectious prions may help lead to the design of diagnostic and therapeutic strategies for these diseases, as well as others associated with the accumulation of misfolded proteins (Parkinson's and Huntington's diseases, type-2 diabetes, and many others). Recent breakthroughs in research on Alzheimer's and other diseases that mostly manifest late in life provide new hope for the enjoyment of healthy aging.

About the Authors

Rodrigo Morales, Ph.D. is an associate professor of neurology at UTHealth McGovern Medical School. He holds a Ph.D. in biology and a B.Sc. in biochemistry, both from the University of Chile. Dr. Morales has been working in the field of protein misfolding disorders for the last 15 years. He has contributed more than 35 research articles to journals in neurobiology, primarily on the molecular basis of prion strains and how single strains are transmitted to multiple animal species. He has also published articles on the prion-like nature of the amyloid-beta peptide in Alzheimer's disease. For inquiries about Dr. Morales' research, contact him at Rodrigo.MoralesLoyola@uth.tmc.edu.

Ruben Gomez-Gutierrez, M.Sc. is a Ph.D. candidate at the University of Malaga in Spain and a research assistant at McGovern Medical School. He holds an M.Sc. in cellular and molecular biology and a B.Sc. in biology from the University of Malaga. He is currently deciphering novel triggering events of Alzheimer's disease as part of his Ph.D. project. Over the past year, he has successfully established international collaborations for Dr. Morales's laboratory.

Upcoming Events

UTHealth NRC 2019 Distinguished Lecture in the Neurosciences

Making Learning Stick: The Science of Successful Learning

Henry Roediger, III, Ph.D.
James S. McDonnell Distinguished University Professor
Professor of Psychological & Brain Sciences
Washington University in St. Louis

Thursday, February 28, 2019, 4 p.m.

UTHealth McGovern Medical School Building, 2.006
6431 Fannin St, Houston, TX 77030

UTHealth NRC 2019 Brain Night for Kids

Thursday, March 14, 2019, 6 to 8 p.m.

John P. McGovern Museum of Health and Medical Science in the Museum District of Houston
1515 Hermann Dr., Houston, TX 77004

This *free* annual event gives elementary school children and their families an opportunity to learn about neuroscience through experiments and activities designed *JUST FOR KIDS!*

UTHealth NRC 2019 Public Forum:

Maintaining Brain Health Across the Life Span

Saturday, April 13, 2019, 10:30 a.m. to noon

The UTHealth Cooley University Life Center
7440 Cambridge St., Houston, TX 77054

UTHealth NRC experts will discuss brain health, disorders, and research and address questions from the audience.

Moderator: **Thomas D. Meyer, Ph.D.,** associate professor, director of the Psychological Intervention & Research Program on Mood Spectrum Disorders, and co-director of the UTHealth Brain Collection for Research in Psychiatric Disorders

Panelists: **Jennifer Beauchamp, Ph.D., R.N.,** associate professor and holder of the Nancy B. Willerson Distinguished Professorship in the UTHealth Cizik School of Nursing

Summer Ott, Psy.D., assistant professor in the Department of Orthopedic Surgery and director of the Concussion Program at Memorial Hermann Ironman Sports Medicine Institute

Joy Schmitz, Ph.D., the Louis A. Faillace Professor and director of the Center for Neurobehavioral Research on Addiction at UTHealth

Paul Schulz, M.D., the Rick McCord Professor in Neurology and director of the UTHealth Memory Disorders and Dementia Clinic

This event is free and open to the public. Register online at https://med.uth.edu/nrc/24th-annual-neuroscience-public-forum/.

We welcome notices of your neuroscience seminars, grand rounds, research colloquia, and conferences (sponsored by UTHealth, the Texas Medical Center, and area institutions) for our calendar (https://med.uth.edu/nrc/eventcal/). Please send the event name, contact details, date, time, and place to UTHealth.NRC@uth.tmc.edu.

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Questions? Comments?

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