2016
MetLife Foundation

AWARDS
FOR MEDICAL
RESEARCH IN
ALZHEIMER’S
DISEASE

thirty years of excellence
Innovation Meets Dedication

Randall Bateman, MD

Charles F. and Joanne Knight Distinguished Professor of Neurology, Washington University School of Medicine, in St. Louis

As both a research scientist and practicing clinician, Dr. Randall Bateman has become one of the world leaders in Alzheimer’s disease research, significantly advancing the field from the bench all the way to the bedside. Before Dr. Bateman provided his breakthrough contributions to the study of how Alzheimer’s disease (AD) begins and progresses, virtually everything known was based on animal models or the examination of the brains of AD patients who had died. Dr. Bateman led the development of a technique known as stable isotope-linked kinetics (SILK) that made it possible to measure central nervous system (CNS) proteins in living people. This game-changing research provided fundamental advances in our understanding of the metabolism of CNS proteins, including the normal production and removal of amyloid-beta (Aß), and how removal of Aß is impaired in Alzheimer’s patients.

Now, Dr. Bateman and his colleagues are studying whether alterations in the body’s ability to clear Aß can be used to predict the likely development of the disease years before symptoms become apparent. The goal of this work is to prevent damage to brain cells through early intervention.

Dr. Bateman explains, “We understand the process of how amyloid-beta develops over time in living people. We have clarified the relationship between the risk factor of age, the biomarker of Aß deposition, and real-time Aß processing through Aß SILK.”

Dr. Bateman’s SILK technique is used extensively by pharmaceutical companies to evaluate the effects of drugs targeted to Aß production and removal.

While these achievements alone could qualify Dr. Bateman for a MetLife Foundation Award, they are a small sample of the contributions that he continues to make to the field. In the lab, Dr. Bateman is building on his landmark SILK studies of amyloid-beta activity by developing a SILK method for measuring and studying central nervous system tau protein pathology. This work will enable the design of therapies targeted to the other physiologic hallmark of AD: the twisted and tangled strands of abnormal tau that destroy the microtubular structure of brain cells.

Dr. Bateman’s lab also is leading a new area of inquiry into the relationships among sleep patterns, aging, and Aß production and deposition. His team has determined that amyloid levels increase when subjects are awake and decrease during periods of sleep, and that Aß removal appears to be enhanced during sleep. Further, these normal Aß circadian patterns are attenuated in the presence of amyloid deposition. These findings have demonstrated a direct link between aging and amyloid-related pathological effects on the normal circadian rhythms of Aß production and removal.

“Why circadian patterns are related to Aß levels is not yet known, nor is it known whether the quality of sleep is a factor in the flushing of Aß levels,” Dr. Bateman notes. “But this area of inquiry begins a new chapter in the discussion of the body’s natural protective factors against AD and how preventive therapies can help preserve and strengthen those factors.”

Beyond the lab, Dr. Bateman has focused his work as a clinician on disease prevention. He is the director and principal investigator of the Dominant Inherited Alzheimer’s Network Trial Unit (DIAN-TU)—a partnership of academic researchers, the National Institute on Aging, the DIAN Pharma Consortium, regulatory agencies, and patient advocacy groups all working together to stop AD before it starts. DIAN-TU is engaged in the first global AD prevention trial using anti-amyloid drugs in people who are not exhibiting symptoms but have a high genetic risk of developing the disease.

The DIAN-TU is the coordinating center for a trial involving over one hundred doctors, nurses, scientists, and clinicians worldwide focused on clinical methods to prevent loss of brain function by intervening long before symptoms of AD appear. The study tracks prevention or progression in participant families whose members carry gene mutations that dramatically increase their likelihood of developing Alzheimer’s disease. The trial is unique in that it will test multiple drugs rather than the usual practice of testing a single drug at a time.

Dr. Bateman recognizes the importance of this award from MetLife Foundation to further the important work he is doing. “The award will speed up the tau kinetics assay and other early stage novel developments necessary to get the data we need to do studies of tau-based therapies. We are developing a comprehensive picture of the time frame and events that lead to the development of symptomatic AD and dementia. The studies of both dominantly inherited and sporadic AD form a solid foundation for current and future prevention trials.”
Ask Dr. Christian Haass what point he considers most important to make in a brief overview of his award-winning research, and he says, “Make sure you mention that without the support of my colleagues Konrad Beyreuther and Dennis Selkoe, I would not be receiving this award.”

While the MetLife Foundation Award for Medical Research in Alzheimer’s disease is in recognition of the breakthrough research Dr. Haass has led over the last twenty years, he is quick to point out that when he started, he was a molecular biologist in a field dominated by neurologists. The support of Drs. Beyreuther and Selkoe was essential to the advancement of his area of inquiry. “Dr. Selkoe literally rebuilt his laboratory to support molecular biological research.”

His mentors’ investments have paid huge dividends. Dr. Haass’s work has redefined research of neurological diseases, and his findings have translated directly into the development of promising drug therapies.

When Dr. Haass started his research, very little was known about the cellular and molecular mechanisms involved in the pathology of Alzheimer’s disease (AD). He was among the first to show that the amyloid-beta peptide (Aß) was produced as part of normal, healthy human biology. This finding was a major breakthrough for the entire field of Alzheimer’s disease research. It has contributed to:

1) a broad understanding of the molecular principles behind the body’s creation of Aß;
2) the identification of the enzymes involved in the creation process;
3) the development of breakthrough drugs designed to inhibit Aß production and aggregation.

A detailed understanding of the functions and properties of enzymes implicated in AD pathology is critical if scientists are to avoid potentially harmful side effects of therapies that target the healthy expression of these enzymes. Among Dr. Haass’s many accomplishments is the first demonstration that one of these enzymes, beta-secretase, is critical to the proper regulation of the electrical insulation of brain cells. Inhibiting beta-secretase’s work could disrupt an intracellular signaling pathway that is critical to the development of healthy neurons. Important findings like this are helping to ensure that promising treatments currently under development and testing do not have potentially harmful side effects.

Dr. Haass also has pioneered research in another promising area of inquiry: the body’s natural clearing of Aß. A protein called Triggering Receptor Expressed on Myeloid cells 2, or TREM2, plays a role in the clearing of cellular waste material. Dr. Haass has demonstrated how a mutation in the gene responsible for encoding TREM2 results in the protein losing its ability to absorb and remove potentially dangerous waste material in and around cells. Improperly coded TREM2 may also lead to an increase in the amount of misfolded amyloid in the body. More Aß means an increased risk that these peptides will find one another and aggregate into the plaques characteristic of Alzheimer’s. There is still more testing to do on TREM2, but if Dr. Haass’s hypothesis holds, a patient’s level of soluble TREM2 may become a biomarker for early cell death.

“Our current belief,” Dr. Haass explains, “is that increased levels of TREM2 in the system may be an indication that the body has begun building up its defense against Aß aggregation. There appears to be a significant decrease in TREM2 as the disease progresses, which may indicate that the body has given up the fight. Maintaining healthy levels of properly encoded TREM2 may prove to be an important first line of defense against amyloid plaque formation.”

With new AD therapies at critical stages of testing, Dr. Haass’s deepening understanding of the disease’s molecular biology is needed to ensure that treatments are both effective and safe. Dr. Haass also is the co-author of a forthcoming paper in Nature currently in press, which may shed new light on APP function.

“The beauty of the MetLife Foundation award is that we can put the money toward the work we feel is most important. The award is very timely because there is such urgency to the work we are doing with TREM2,” he notes. “Any drugs that we develop must enhance, not inhibit, the body’s natural defenses. With so much at stake for people who have or are at risk of developing AD, it is important that we get this right.”
Mathias Jucker, PhD, and Lary C. Walker, PhD

New Discoveries and Collaborations

The opening sentence of their nomination form reads, "Rarely in the course of discovery does a concept emerge that suddenly consolidates our thinking about the causation of seemingly unrelated diseases." Drs. Lary Walker and Mathias Jucker have pioneered just such a unifying principle—seeded protein aggregation—based on their answer to a provocative question: What can mad cow disease tell us about neurodegenerative diseases like Alzheimer’s and Parkinson’s? Dr. Walker had published a paper that put forward the idea that the toxic proteins characteristic of Alzheimer’s behave very much like prions. A prion—short for proteinaceous infectious particle—is a misfolded version of a protein normally found in nerve cells. Prions have long been identified as the infectious agents that cause mad cow and other deadly diseases. Prions interact with healthy proteins causing them to misfold and clump together, thereby spreading the disease. This chain reaction eventually destroys entire regions of the infected brain.

When sticky clumps of misfolded amyloid protein were found strangling neurons in the brains of Alzheimer’s victims, scientists began to speculate about the possible parallels between the processes of replication and aggregation of misfolded proteins in prion diseases and non-prion neurodegenerative diseases like Alzheimer’s. Dr. Walker posited that this seeding process—whereby one prion serves as a template for the creation of other misfolded proteins—could be the same mechanism by which misfolded amyloid-beta proteins replicate and spread to various regions of the brain.

Dr. Jucker immediately saw the possibilities of what he calls “a cool idea,” and beginning in the late-1990s the duo took advantage of new mouse models genetically engineered to produce the precursor protein from which the human amyloid-beta fragment is created. In a milestone 2006 paper in Science and a series of subsequent reports, they were able to unequivocally demonstrate the self-propagating (prion-like) features of aggregated amyloid-beta protein.

Their work has resulted in three critical findings:

1. They established that seeds of misfolded amyloid-beta underlie both the emergence and the progression of amyloid-beta plaques in the brains of experimental animals.
2. They found evidence that variations in the size and molecular architecture of amyloid-beta seeds can profoundly influence their ability to cause disease.
3. They showed that small, soluble aggregates of amyloid-beta are especially potent seeds, which means their presence could be an early indication of a person’s likelihood to develop Alzheimer’s. It also makes these seeds prime targets for therapeutic intervention.

The prion-like mechanism encapsulates a lot of information in a simple idea, and was rapidly expanded to include key proteins involved in other age-related neurodegenerative diseases. Knowing the mechanism by which the toxic proteins spread from one region of the brain to another allows researchers to focus attention on the risk factors that lead to the formation of the seed proteins and on how those factors interact over time to cause the disease.

A major focus of Drs. Jucker and Walker’s work going forward will be on the different strains of amyloid-beta seeds they have discovered. Just as different prions cause different diseases, strains of amyloid-beta have different characteristics, with some being more toxic than others. The research teams will go deeper into the biochemistry of how toxic amyloid-beta is formed and how it can be stopped before it triggers its long, lethal chain reaction.

Having two labs focused on aspects of the same mechanism enables them to move more quickly from this pioneering concept to practical applications. “These discoveries have put us in the world of diagnostics and therapy,” observes Dr. Jucker. “As you get a little older you find yourself wanting to do work that has significance beyond the lab, work that is clinically relevant. We’re there now. This is truly translational work.”

A lot of important research remains. However, by establishing seeded protein aggregation as a fundamental pathogenic principle, the work of Drs. Walker and Jucker stands to consolidate and expand to include key proteins involved in other age-related neurodegenerative diseases.

Dr. Walker expressed the team’s appreciation for MetLife Foundation’s award. “I’ve found that private sources of funding such as MetLife tend to recognize the significance of certain areas of inquiry before organizations like the National Institutes of Health do. They allow for more creative and original research. I wish there were more like them.”
In 1999 Dr. Riqiang Yan published research in Nature that would establish beta-site amyloid precursor protein cleaving enzyme 1—also called BACE1—as a prime target for cutting off the pathological march of Alzheimer’s disease. BACE1 is an enzyme that cuts the amyloid precursor protein into fragments that can lead to the creation of the toxic amyloid-beta known to form the familiar plaques of Alzheimer’s. Fifteen years after the discovery of BACE1, many scientists believe it has established itself as the only viable drug target for inhibiting amyloid-beta production and thereby reducing or even stopping the aggregation of amyloid deposits in the brain.

Ironically, a couple of years before his breakthrough discovery, Dr. Yan wasn’t even doing Alzheimer’s research. The pharmaceutical company he was working for moved its research on lung inflammation offshore. Dr. Yan’s team needed to find a new area of inquiry. Knowing the long-term healthcare and economic threats the disease posed not only in the U.S. but internationally, the team turned its attention to Alzheimer’s.

“We knew amyloid plaque was the big target,” explains Dr. Yan. “The logical step was to stop amyloid-beta generation. When we started, Alzheimer’s disease (AD) research was largely on the cellular level. We wanted to find the molecule that was at work. We identified four protein-cleaving enzymes that had not been previously studied and tested each to see if they generated beta-amyloid peptide. We had our answer pretty quickly. It surprised us and the industry.”

A little over a year after their research began, Dr. Yan’s team published their game-changing paper, featuring work that corroborated and expanded upon the work of BACE1 co-discoverer and a fellow MetLife Foundation Award for Medical Research winner Dr. Robert Vassar. Ask Dr. Yan how he and his team were able to move so quickly, and he’s likely to say they got lucky. Ask one of his peers, and they will credit the brilliance of his original hypothesis and the elegance of his research strategy.

As a result of his significant contributions to AD research, Dr. Yan was recruited to the Cleveland Clinic’s Lerner Research Institute in 2003. He has become one of the foremost experts on multiple aspects of BACE1 functionality. For example, he discovered that BACE1 regulates myelination, the process by which myelin forms a protective “sheath” around the fibers of brain cells.

As pharmaceutical companies began aggressive pursuit of drugs designed to inhibit BACE1 activity, Dr. Yan’s team was the first to demonstrate potential side effects of knocking out BACE1 completely. He was the first to discover that mice without BACE1 develop spontaneous epileptic seizures—a discovery that was later verified by others. He has also associated too little BACE1 with: A decrease in the amount of myelin in the brain; Impaired ability of the central nervous system to create new myelin sheaths when the sheaths of nerve fibers are damaged; Shifts in the way stem cells in the central nervous system differentiate into the various types of brain cells needed for maintenance of a healthy adult brain.

Dr. Yan has been awarded 26 patents for his original discovery of BACE1, its substrates, and assays. His ongoing studies of BACE1 continue to provide important guidance for the safe development of therapeutic BACE1 inhibitors for patients with Alzheimer’s disease.

More recently he has demonstrated that the BACE2 gene cleaves the amyloid-β precursor protein (APP) in such a way as to prevent amyloid-beta (Aβ) formation. His research suggests that targeting BACE2 activity is likely an alternative approach for reducing the accumulation of amyloid proteins.

Dr. Yan’s immediate goal remains figuring out how to retain the positive aspects of BACE1 activities while decreasing the protein cleaving that contributes to the development of amyloid plaques. Several drug candidates based on Dr. Yan’s discoveries are now in clinical trials.

“The MetLife Foundation award,” Dr. Yan says, “will help us investigate the biological function of BACE1, especially looking at how the reticulon 3 protein naturally reduces BACE1 activity. Perhaps modestly increasing the activity of this or other natural BACE1 modulators will prove to be a long-term preventive treatment for Alzheimer’s.”
The Power of Basic Research

Yueming Li, PhD

After receiving his doctorate in comparative biochemistry from the University of California, Berkeley, and postdoctoral training from Harvard Medical School, Dr. Li spent many years in the Merck Research Laboratories doing important but clinically focused work on neurodegenerative diseases. “At first, I liked that my work had direct clinical applications,” said Dr. Li. “I did a lot of research and made a good contribution to drug development.”

However, he decided to return to academia because he missed the freedom of performing research that isn’t directly tied to drug development. “The advantage of basic research,” Dr. Li says, “is that it can move in directions that you never planned on.”

He believes he has found the best of both worlds at Memorial Sloan-Kettering Cancer Center, where he and his team can do both basic research and drug development. “I find this translational element to be essential.”

Dr. Li made his mark in Alzheimer’s disease research with breakthrough studies of γ-secretase, an enzyme that cleaves the amyloid precursor protein into the fragments that form the deadly plaques characteristic of Alzheimer’s. When he first started looking at γ-secretase, research was being done at the cellular level. Dr. Li developed the first process for studying γ-secretase in the test tube, where he could break down the biochemistry of the enzyme.

In 2000, his team’s work resulted in the publication of a paper in Nature that opened a new era for the investigation of γ-secretase’s role in the pathology of Alzheimer’s. Their findings provided the first compelling biochemical evidence that γ-secretase activity is triggered by subunits within the γ-secretase complex called presenilin.

In 2010, his lab made another breakthrough in γ-secretase research. His team has reconstituted γ-secretase by using bacteria-expressed recombinant proteins and provided the final proof that presenilin is indeed γ-secretase. And it provided a unique platform for further study of the structure and function of γ-secretase at both the molecular and atomic level, which was previously impossible. This work is considered a landmark in the field.

Dr. Li has since turned his attention to how the processing of the amyloid precursor protein can be changed through modulation of γ-secretase activity. “We’re focusing on gamma modulation that is specific to the cleavage of the amyloid precursor protein at the 42 site, Notch receptors and other substrates. We want to use modulators to retain physiological role and decrease pathological role.”

Dr. Li is drawn to research on neurodegenerative diseases because he is passionate about aging-related diseases. “I believe my expertise in chemical biology provides me with an opportunity to make a significant contribution to a field in critical need of breakthrough discoveries.”

The MetLife Foundation Award for Medical Research comes at an opportune time. It will support his team’s new effort to discover biomarkers for the disease and to examine how γ-secretase’s role and activity change with age – a critical Alzheimer’s risk factor.

“The award supports basic research,” he says, “which is about taking the risks necessary to return life-saving rewards. Right now I have a good team in place, and I’m excited about our prospects for doing some important work.”

Dr. Li’s other honors include the Top Performance Award-Merck Research Laboratory, a “Hot Paper” by The Scientist, and the Zenith-Fellows Award from the Alzheimer’s Association.
2013

The Power of Basic Research

Lennart Mucke, MD

Director, Gladstone Institute of Neurological Disease
Joseph B. Martin Distinguished Professor of Neuroscience and Professor of Neurology
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For people familiar with the research of the last 25 years, it may seem to be taking scientists a long time to move from the identification of the genetic risk factors associated with Alzheimer’s disease to developing pills to hinder or halt its progression. The reason, according to Dr. Mucke, is that the paths from genetic changes to neurological dysfunction are not well understood. “There is no easy answer to this complex problem,” he explains. “You need to attack it from many angles. To date research has been dominated by what can be studied under a microscope. But much of the pathological activity can’t be seen in fixed brain sections.”

Appreciating the complexity of Alzheimer’s, Dr. Mucke has pursued a multidisciplinary, highly collaborative approach to investigating both the structural and the functional aspects of the disease. While the microscope remains a vital tool in his research arsenal, Dr. Mucke has used a variety of approaches—including electrophysiological analyses of brain rhythms and synaptic functions, behavioral assays and newly identified molecular biomarkers—to achieve the most complete picture possible of what is going on. As a result, his team has provided fascinating new insights into the mechanisms underlying the cognitive dysfunction associated with Alzheimer’s disease. And they have identified novel therapeutic strategies to block these mechanisms.

For example, Dr. Mucke’s team showed that the activities of three proteins associated with Alzheimer’s—amyloid-beta, apoE4 and tau—can interfere with the communication among brain cells. These proteins’ activities disrupt the delicate balance between the triggering and inhibiting of brain cell activities required to maintain healthy brain functions. Of particular importance is the team’s discovery that the interactions of these proteins can begin compromising cell network integrity before the development of the classic amyloid plaques and tau tangles that have become synonymous with Alzheimer’s. Of particular interest is that amyloid-beta impairs the activity of critical inhibitory cells, which can be viewed as conductors of the large neuronal orchestrations they regulate. “Disrupt the conductor,” Dr. Mucke says, “and instead of finely tuned music, what comes out is muddled noise. We want to find a way to protect and strengthen the conductor.”

Other researchers have noted that brains afflicted with Alzheimer’s exhibit hyperactive neuronal activity. Most hypothesized that this excitation of neurons was compensating for cells that had been compromised or killed by the disease. Dr. Mucke’s findings suggest that some of this hyperactivation is not compensatory; it is a primary phenomenon resulting from the buildup of amyloid proteins that can precede full-blown Alzheimer’s. “The brains of Alzheimer patients appear to be ‘trigger happy,’” he notes, “they have a tendency to go into abnormal rhythms. This disruption probably contributes to cognitive impairments. We’re trying to find out how it comes about and how to prevent it.”

Dr. Mucke’s early results led to experiments designed to address whether blocking abnormal network activity could be useful from a therapeutic perspective. Improving neurotransmission by counteracting the disease causing activities that amyloid proteins and tau do together and blocking their detrimental effects on network activity have proven to be areas of great promise.

Dr. Mucke is deeply appreciative of the impact the MetLife Foundation Award for Medical Research will have on his work. “The timing couldn’t be better. Our lab has two papers under review that focus on the role of a very promising cognition-enhancing factor. The award will help us accelerate and intensify our efforts, so we can turn our latest discoveries into potential therapies for this devastating illness. I also hope that the award will help my Institute attract additional support for these exciting studies.”

Dr. Mucke was also a 2002 MetLife Foundation Promising Investigator Award winner. Among Dr. Mucke’s other awards are the Khalid Iqbal Lifetime Achievement Award and the Zenith Award from the Alzheimer’s Association, as well as the Potamkin Prize from the American Academy of Neurology.
Looking Back to Predict the Future

Christine Van Broeckhoven, PhD, DSc

After 29 years of groundbreaking molecular genetics research, Professor Christine Van Broeckhoven remains naïve. “I am a scientist and very rational,” she explains, “however, I believe it is important for even the most reasonable mind to remain a little naïve, because then you keep the ability to be surprised, to challenge your own assumptions.”

When Prof. Van Broeckhoven began her research back in 1983, there was no genetic research being done on Alzheimer’s disease. She was a molecular biologist and had not considered genetics as an area of focus. Then a colleague neurologist Jan Gheuens mentioned the work of Dr. James Gusella that had led to the identification of the gene responsible for Huntington’s disease. Dr. Gheuens suggested she investigate the genetics of early-onset AD.

“What convinced me to take on the challenge was the fact that our brain is what is unique about being human. Neurodegenerative diseases like Alzheimer’s take away our basic humanity. I wanted to shed light on the biological processes of this devastating disease.”

Under her visionary leadership, an ever-growing team of cross-disciplinary researchers has made many seminal contributions to our understanding of the molecular mechanisms that determine the onset and progression of AD. Those contributions include identification of the first gene ever linked to Alzheimer’s dementia, the amyloid precursor protein, or APP. She went on to help identify the presenilin-1 gene on chromosome 14 as an additional gene involved in AD. Her team also demonstrated that the apolipoprotein E4 is not only a risk factor for late-onset AD but also for early-onset forms. These critical discoveries, among many others, have provided the basis for follow-on research into the key proteins involved in the various pathological cascades characteristic of the disease.

Prof. Van Broeckhoven has recently broadened her work to include investigations into the genetics of other neurodegenerative brain diseases, such as frontal temporal lobar degeneration, or FTLD, and Parkinson’s. This broader view was inspired by the fact that the effects these diseases have on various areas of the brain are not neatly segmented by clinical subcategory. Prof. Van Broeckhoven believes the next breakthrough in the identification of targets for therapy will come about through intense collaboration among geneticists, pathologists, and clinicians across the spectrum of brain disorders.

Her goal is to identify as many risk genes for various neurodegenerative diseases as possible and then find patterns, common themes. She believes these themes will lead scientists to the biological pathways that represent the greatest biological risk factors, such as perhaps the way a body metabolizes lipids, or maybe a specific breakdown in the immune system. Finding the combination of risk factors most likely to predispose someone to the disease and knowing how those risk factors manifest biologically can lead to proactive, preventive therapies.

“We have therapies that prevent the buildup of plaque in arteries. These drugs are known to reduce a specific risk factor for the development of heart disease. I believe one day we will have similar therapies that ward off the processes leading to the systematic killing of brain cells in the aging brain.”

Prof. Van Broeckhoven is no stranger to awards ceremonies. She was earned multiple honors in each of the last three decades, including the Potamkin Prize from the American Academy of Neurology (1993), the Zenith Award from the Alzheimer’s Association (2005), and the European Inventor Award in the category of Research (2011). She is grateful to these awards for, in her words, “giving volume to my voice.”
Dr. Jack has been helping to identify and validate brain imaging markers on the path to symptomatic Alzheimer’s disease for twenty years. Using two reliable windows into the development of the disease prior to the onset of clinical symptoms—brain imaging and cerebrospinal fluid analysis, or CSF—he has introduced methods for staging the disease’s severity, predicting future decline, and measuring disease progression. It is extremely difficult to overstate Dr. Jack’s impact on Alzheimer’s disease research, particularly and most importantly his recent influence.

Over the past several years Dr. Jack has focused on studies integrating multiple biomarkers from both imaging and CSF. What he and his multidisciplinary team of colleagues have discovered about the fundamental mechanisms of AD has led many researchers to rethink their concepts of the biological origins of the disease and the clinical criteria that define it.

Dr. Jack has a proposed model in which amyloid biomarkers first depart from normality years before the first significant clinical symptoms of Alzheimer’s appear. Meanwhile, biomarkers indicating injury to brain cells appear much closer to but still preceding the onset of overt clinical symptoms. Dr. Jack’s measurements show that while the increase in abnormal brain amyloid deposits before and during the appearance of symptoms is a necessary aspect of the disease, it is not sufficient to produce the cognitive decline characteristic of AD dementia.

Dr. Jack published an expanded version of the disease biomarker model in 2010. The model incorporates five well-validated AD biomarkers into a comprehensive sequence of events over time as an individual progresses from cognitively normal in middle age to dementia in old age. In less than two years, the model became a standard reference in presentations at virtually every national and international meeting on AD.

Dr. Jack’s findings are significant in three ways:

1. They force researchers to reconceptualize the biology of Alzheimer’s disease—scientists must understand the different pathological cascades underlying the disease’s symptoms and strive to understand how they work together.

2. Clinical trials will be influenced by a better understanding of the different stages of the disease as characterized by the various cascades. Attempts to prevent the disease can be targeted to the beginnings of each cascade.

3. He has forced a rethinking of the clinical criteria that define the disease. Until 2011, the National Institutes of Health did not include biomarkers in their diagnostic criteria. Their newly published criteria not only include biomarkers relevant to clinical diagnosis, but also acknowledge indicators of preclinical AD. Staging of preclinical AD in the new NIH criteria is based on Dr. Jack’s model.

Most recently, Dr. Jack has turned his attention to outlining a step by step approach for establishing standards for the various imaging AD biomarkers just as there are standards for such health risk factors as blood pressure and cholesterol levels.

“Currently,” Dr. Jack notes, “published standards for healthy brain volume measurement vary by 250%. The processes differ, so the results differ.” If doctors have accurate, agreed upon measurements for biomarkers such as normal versus at-risk brain volume or amyloid levels, they would be in a position to prescribe strategies for preventing or at least delaying the pathological progression of the disease.

Because of its profound importance, Dr. Jack’s work has earned him international attention and honors, including an Alzheimer’s Disease Neuroimaging Award from the Alzheimer’s Association, the Career Research Award from the American Society of Neuroradiology, the Potamkin Prize from the American Academy of Neurology, and a Gold Medal from the International Society of Magnetic Resonance in Medicine.
For nearly 40 years, Dr. Marcus Raichle has been producing pioneering brain imaging research. Since joining the faculty of Washington University in St. Louis in 1971, he helped develop the fundamental set of tools that allow researchers to visualize mental activity in the human brain.

Among Dr. Raichle’s major accomplishments was his lab’s discovery of a brain region now referred to as the default mode network. Dr. Raichle’s team observed that if you image someone’s brain while they are not engaged with the external world, a specific brain activity pattern will emerge. The activity pattern is distributed across the brain, including memory systems and frontal systems. They referred to these specific regions as being part of a default mode network because these are the areas our brain uses when we are not engaged in task-related activity.

More recently researchers have described a novel brain pathway they think represents an important component of the brain’s memory system. The critical discovery was that areas in this newly observed memory pathway overlap with the brain areas of the default network. What they have observed in middle-aged subjects is that the pathways we use during our default activity coincide with areas where amyloid deposition occurs in 80 year olds. Amyloid was in exactly the areas Dr. Raichle was studying.

“The default network seems to be a target of Alzheimer’s disease, which I found stunning. Why does Alzheimer’s attack that region?” Dr. Raichle asks. “The simple answer is, we don’t know.”

These observations have given rise to a hypothesis: The brain activity that occurs much of the time throughout our lives, and the breaking down and building up of substances that these activities encourage, may set the stage for the eventual deposition of amyloid.

Dr. Raichle’s current research focuses on the intrinsic functional activity of the brain in its default mode as distinct from the activity evoked by behavioral or task-related events. His team’s measurements of brain energy consumption indicate that over 95% of the energy used by the brain is burned by this default activity.

“Understanding intrinsic functional activity must be at least as important to understanding brain function as the more traditional task-related research has been,” Dr. Raichle observes. Though the picture is far from complete, the mapping Dr. Raichle and his team has done suggests novel ways to view the functions and metabolism of the brain that precede the development of Alzheimer’s disease. Most recently his team has turned its attention to observed changes in brain glucose metabolism in people at risk for Alzheimer’s disease.

“What’s been particularly interesting to us of late has been the observation that the nature of metabolism in the default mode network is distinct from other brain areas not just in amount but also in just how the brain’s primary fuel, glucose, is used.”

Dr. Raichle’s work is recognized for being highly innovative and multidisciplinary, earning him numerous honors and awards. He has been a catalyst for research in the social and medical sciences, as well as systems neuroscience, neurophysiology, cell biology, metabolism and genetics. His work has been cited nearly 40,000 times worldwide.
The major interest of Dr. Buckner’s laboratory is the study of human thought and its disruption in disease. Dr. Buckner’s breakthrough contribution to his field came in the mid-1990s when he developed a new technique for tracking brain activity. The technique, called event-related functional magnetic resonance imaging, improved on previous imaging methods so researchers could observe a memory materializing in a matter of seconds. Using his new technique, Dr. Buckner led an extensive research effort to characterize brain systems important to memory and cognition.

One of his most significant findings was the identification of activity patterns in specific regions of the brain during memorization tests that can be used to predict if someone will remember an individual word. Essentially, Dr. Buckner is able to read his subjects minds.

Using these methods, he went on to map a system across various areas of the brain that specializes in memory function. He used these maps of brain activity in healthy individuals to form a foundational understanding of the degeneration of brain cells that takes place during Alzheimer’s disease.

Dr. Buckner’s research suggests that memory loss in normal aging and memory loss in Alzheimer’s are different. He found what he calls distinct cascades, or patterns of disruption. Normal aging results in subtle and slow progression of changes in communication patterns between regions of the brain. The Alzheimer’s cascade progresses much more quickly and targets regions specific to the default network, including brain systems important to memory.

One of Dr. Buckner’s most surprising discoveries is that the regions we normally use when we are at rest — referred to as the default network—are those most vulnerable to Alzheimer’s pathology. In a seminal study in 2005, he showed that activity in the default network in healthy young adults is eerily similar to the pattern of Alzheimer’s pathology in the preclinical stages of the disease, as well as to the pattern of brain loss that emerges as the disease progresses. This suggests that perfectly normal activity or metabolism in someone vulnerable to Alzheimer’s may accelerate the early stages of the disease’s development.

“Brain-imaging advances are finally allowing neuroscientists to distinguish, for the first time, the aging brain from the Alzheimer’s brain,” Dr. Buckner says. “In the past, when researchers studied memory in normal aging, they probably had in their samples people whose early Alzheimer’s disease was undetected, confounding the results.”

Dr. Buckner’s lab is currently exploring why activity and metabolism patterns in some individuals may place them at risk for Alzheimer’s disease while some individuals with hereditary risk turn out to be resilient to the disease. One goal of Buckner’s research is to detect Alzheimer’s disease in the brains of elderly people before they develop symptoms.

“If there were a way to see early disease,” he says, “clinicians and investigators would be able to monitor the effects of interventions that might either delay or prevent the patient’s decline.”

Dr. Buckner’s research is pushing back the exploration of Alzheimer’s disease from the beginning points of the disease pathology and forming an understanding of the stage-setting conditions that may be the precursors to the earliest stages of the disease. With all of the new methods of study available today, he is confident that as more of us live into our 90s, we will be able to do so with our memories intact.
Todd Golde came to the study of Alzheimer’s disease early in his medical career. His PhD thesis was performed in the lab of renowned Alzheimer’s researcher, Dr. Steven Younkin. Dr. Golde published a series of important papers out of that lab in the early 1990s. His work showed that amyloid beta peptides are normally derived protein from the processing of the amyloid beta precursor protein, or APP. His work went on to show that mutant forms of APP alter its normal processing and contribute to the increased production of a toxic “longer” form of the amyloid beta protein that aggregates much more quickly than shorter forms. Later in his career, he demonstrated in mice that the shorter forms of amyloid beta may actually inhibit aggregation of amyloid beta strands.

Based on his recent research with mouse models, Dr. Golde has concluded that Alzheimer’s may need to be treated much like using drugs called statins, which are used to prevent the development of heart disease caused by high levels of bad cholesterol. Dr. Golde believes a similar approach should be taken with Alzheimer’s. “I will place a bet with a high degree of confidence,” he has stated, “that we will have preventive therapy for AD long before we have stem cell or another type of therapy that truly and completely reverses clinical dementia.”

The research he has been doing in collaboration with Dr. Edward Koo may hold the key to the development of a preventive therapy. Working together, Dr. Golde’s and Dr. Koo’s laboratories have found that gamma-secretase modulators, or GSMS, can actually shift the production of amyloid beta from the “bad” longer forms to the “good” shorter form, much the same way heart therapies look to increase the production of good cholesterol while reducing the amount of bad cholesterol in the system.

GSMS appear to modulate the types of amyloid beta peptides that cells produce and thereby significantly impact their accumulation in the brain. This means that these compounds may do three things that are beneficial with respect to the prevention of Alzheimer’s disease: They decrease the production of bad amyloid beta, they block its accumulation into deadly plaques and they increase production of good amyloid beta peptides, which may further inhibit bad amyloid beta accumulation.

“The tools are there,” says Golde. “We understand the disease process well enough. A major key to prevention is developing safe therapies.” These latest discoveries serve to broaden the scientific community’s notion of how drugs and other therapies might safely target Alzheimer’s disease and other degenerative diseases of the brain.

Dr. Golde’s honors include the Paul Beeson Physician Faculty Scholar, Ellison Medical Foundation Young Investigator Award, Outstanding Contributor from the Alzheimer’s Research Forum and a Zenith Award from the Alzheimer’s Association.
In medical school, Dr. Edward Koo had what he calls the “good fortune” to study under neurologist Dr. Albert Heyman and neuropathologist Dr. Stephen Vogel, two of the earliest researchers of Alzheimer’s disease (AD) in the U.S. It was their influence that set him on a path to understand the molecular changes that occur in the brains of Alzheimer’s sufferers.

“My hope has always been to translate findings from basic cell and molecular biology to the clinical setting,” says Koo. His laboratory has several areas of interest regarding Alzheimer’s disease. Perhaps most significant today, is his work on the mechanism of action of gamma-secretase modulators, or GSMs. The work originated from his lab’s studies on what presenilins do in the brain.

Dr. Koo’s work builds on what has been known for some years about how the toxic beta-amyloid protein found strangling brain cells of Alzheimer’s victims is formed. Beta-amyloid is produced from a ubiquitous protein, the amyloid precursor protein, in a two-step process. The first cut is done by an enzyme called beta-secretase. The second cut is made by an enzyme called gamma-secretase, of which presenilins are a key component. If gamma-secretase cuts in the wrong place, the result is the release of the toxic longer form of the amyloid beta peptide.

In 2001, working on a hunch and in collaboration with Dr. Golde, Dr. Koo first reported that the reason certain non-steroid anti-inflammatory drugs, or N-S-A-I-Ds, were being reported as providing protection against the development of AD is because they may influence the activity of the gamma-secretase complex. GSMs reduce the production of the toxic form of beta amyloid peptide. And they seem to do it without blocking other critical gamma-secretase functions.

Based on these discoveries, major pharmaceutical companies around the world began searching for compounds that produce gamma-secretase modulation activity. Experimental GSMs produced by several companies are now just entering human clinical trials.

Dr. Koo is a physician scientist who has had distinguished careers both in teaching and research.

His numerous awards include the Faculty Scholar and Zenith Awards from the Alzheimer’s Association, the Paul Beeson Physician Faculty Scholar in Aging Research and the Mensch of the Year Award from the Alzheimer’s Research Forum.
Since 1989, the research of Drs. Eckhard and Eva-Maria Mandelkow has focused on tau and its relationship to Alzheimer’s disease. Theirs is one of the most unique collaborations in the field. Eckhard is a physicist. Eva-Maria is a medical doctor with several years of practice in university clinics and a PhD in biochemistry. Of the approximately 200 publications the Mandelkows have between them, over 130 of them include both of their names. Their complementary expertise has enabled them to tackle difficult biological questions from different directions.

Eva-Maria has made foundational discoveries pertaining to how tau operates and how its activities are regulated. She has used biological and animal models to make key discoveries about the process by which tau is altered into the toxic form that accumulates in brain cells. Her contributions include:

- The characterization of many of the “abnormal” phosphorylation sites in tau, and the enzymes that are responsible for it;
- The discovery that tau can cause “traffic jams” in neurons because it can prevent the attachment of motor proteins to microtubules. This corresponds to the traffic jams people see in Alzheimer’s neurons; and
- Her creation of unique mouse models.

Eva-Maria’s research is particularly useful for two reasons. First, the expression of tau can be switched on and off, which allows for observation both of the onset of tau pathology and of the recovery after switch-off. Second, the expressed tau in her models comes in two versions, one where tau aggregates particularly rapidly, and one where tau does not aggregate at all. Several important conclusions have been derived using her mouse models.

Meanwhile, Eckhard’s laboratory has focused on the structural and biophysical analysis of tau and the process it goes through. He has used innovative spectroscopic techniques to achieve breakthrough findings with regard to the structure of tau. Eckhard’s contributions include:

- Clarification of the principles of tau aggregation into Alzheimer’s “paired helical filaments.” This work forms the basis for generating cell models of the tau pathology, as well as mouse models;
- Characterization of the loose and open structure of tau that is likely at the heart of its misbehavior in Alzheimer’s and other tau pathologies; and
- His critical structural analysis of proteins and enzymes that interact with tau.

Working together, the Mandelkows have shown that tau toxicity can be prevented in two ways: by switching tau expression off, or by introducing compounds that inhibit the deadly aggregation of tau fibrils. The Mandelkows have searched a library of 200,000 compounds and found a number of inhibitors of several chemical classes that prevent aggregation and toxicity in cell models.
In the late 1980s and early 1990s, Dr. Iwatsubo was a clinical neurologist and then a neuropathologist working on brain tissues donated from victims of Alzheimer’s disease. He was attempting to unravel the mystery of the infamous amyloid plaques that form in the Alzheimer’s brain.

It was well known that accumulation in the brain of amyloid beta protein fragments leads to the formation of the cell destroying plaques that are characteristic of Alzheimer’s. Scientists were also aware that the toxic amyloid beta peptide is formed by a two-step cleaving of the amyloid precursor protein. The first scissor-like cut is done by an enzyme called beta-secretase. The second cut made by an enzyme called gamma-secretase that results in the release of amyloid beta.

In the early 1990s, Dr. Iwatsubo’s lab demonstrated that there was a subtle difference in the length of the amyloid beta peptide that could result from gamma-secretase’s cleaving of amyloid proteins in the membranes of brain cells. The shorter of the two fragments that could result, called amyloid-beta 40, is less harmful and is cleared away. In contrast, Dr. Iwatsubo showed the longer fragment, called amyloid-beta 42, is toxic and accumulates in the brain.

Dr. Iwatsubo discovered it was this longer fragment that significantly affects the formation of fibrils, then plaques which attract inflammatory mediators and result in the amyloid deposits in Alzheimer’s brain tissues. This discovery led his team to further examine the mechanism of production of amyloid beta using molecular biology, biochemistry and structural biology.

Dr. Iwatsubo’s comprehensive and elegant multidisciplinary approach to the study of amyloid beta formation has provided foundational insights to amyloid beta deposition and helped form the contemporary view of the molecular and cellular biology of presenilin. His work helped form the basis of a variety of disease-modifying therapies currently under study. Specifically, Dr. Iwatsubo’s findings have contributed to our understanding of how gamma-secretase inhibitors act on the enzyme to reduce amyloid beta production. Going forward, his team’s short-term goal is to learn more about complex machinery of gamma-secretase to understand how it works as a protein scissors. This improved understanding will contribute to ongoing attempts to develop effective gamma-secretase modulating drugs.

Dr. Iwatsubo also believes an important next step is to promote clinical research. “We wish to promote clinical research to identify and standardize the biomarkers that reflect the disease-modifying effects of Alzheimer’s drugs. This work will serve as the bridge from basic research to the clinics and, hopefully, the development of a safe and effective gamma-secretase inhibitor.”
Dr. Michael Wolfe’s groundbreaking research is the basis of some of the most promising therapeutic developments in Alzheimer’s disease research and it began with a chance conversation in 1994 when he had accepted a new independent faculty position at the University of Tennessee. Just before starting he met a medical researcher at a conference who was working on Alzheimer’s disease. She told him about how amyloid beta protein fragments form the characteristic plaques in the Alzheimer’s brain.

“Given what was known at the time about amyloid and its role in causing Alzheimer’s,” Wolfe remembers, “I thought this seemed like a problem that a chemist could contribute to in a unique and meaningful way.” He began work on designing molecules that would stop amyloid plaque development.

Dr. Wolfe used his new position to initiate a program to discover organic molecules that would serve as probes to understand the molecular basis of Alzheimer’s disease. By 1998, his new team was able to develop the first designed inhibitors of the protein cutting gamma-secretase enzyme. These inhibitors served as chemical probes providing critical information on the mechanism, identity and biological role of the enzyme. Using these chemical probes along with molecular and biochemical approaches, Dr. Wolfe and his colleagues discovered that gamma-secretase is a unique protein complex that plays critical roles in both the pathology of Alzheimer’s and in normal, healthy human development. They were the first to provide evidence that presenilin—one of the proteins in the gamma-secretase complex—was the catalytic component behind the cleaving process that produces amyloid beta. This evidence, focusing attention on presenilin, provided a vital, unifying hypothesis to the various results being reported by Alzheimer’s researchers at the end of the 20th century.

Since first putting forth his hypothesis, Dr. Wolfe has continued his work at Harvard Medical School and Brigham and Women’s Hospital in Boston. His own research as well as his collaborations and related research done by other Awards for Medical Research winners, such as Dennis Selkoe, Bart De Strooper and Sangram Sisodia, have illuminated a novel and complex area of biology that has great implications for Alzheimer’s disease therapy. In fact, Dr. Wolfe’s lab has since found that small, drug-like molecules can stop gamma-secretase from producing amyloid beta while allowing the enzyme to continue its essential function in normal human health.

Dr. Wolfe admits there is a great deal left to be learned about the APP cleaving process and the roles the remnants play in the pathology of AD. But he believes he and others working on unraveling the mystery of gamma-secretase are on the right track. “This award comes at an important time in our research, as gamma-secretase remains a top target for the potential prevention or treatment of Alzheimer’s disease.” Dr. Wolfe’s contributions have been recognized by many awards, including the Zenith Fellows Award from the Alzheimer’s Association.
In 1997, Bart De Strooper had just been promoted to Associate Professor at the University of Leuven in Belgium. As a researcher in neuronal cell biology, he was fascinated by the molecular biological challenge posed by the discovery of the mutation in the presenilin gene that was characteristic of victims of familial Alzheimer’s and its potential relationship to amyloid beta production. Dr. De Strooper’s multinational research group launched studies both of brain cell cultures and of mouse models. In the mice his group knocked out the presenilin gene to see its effect. His studies showed the central role of presenilin in the production of amyloid beta in brain cells. The publication of his findings in Nature magazine in 1998 was the first articulation of the relationship between presenilin and the enzymes that lead to the creation of the toxic amyloid beta peptide. One year later he demonstrated in a follow-up study the essential role of presenilin in the cleavage of the Notch protein, a major regulator of brain and immune function. These two findings have set the stage for worldwide efforts to identify gamma-secretase blockers to treat Alzheimer’s disease without side effects caused by blocking Notch signaling.

Dr. De Strooper’s team went to work on developing a better understanding of the precise balances that regulate on the one hand production and clearance of the toxic Aβ and on the other hand maintain sufficient Notch signaling for survival. They believed that blocking presenilin activity was an excellent target for potential Alzheimer’s treatments. Thus began a decade-long inquiry involving researchers from over 15 different countries that has lead to dramatic improvements in scientists’ understanding of the gamma-secretase protein complex.

Dr. De Strooper’s team has dissected the biological functions of the gamma-secretase complex. His work helped clarify both the promise and problems of therapies designed to inhibit gamma-secretase activity. Most recently they have shown that the gamma complex is actually four similar sub-complexes, and that one of the sub-complexes is more active in the brain. They have further learned that this sub-complex activity can be blocked without major side effects in mouse models. His team is currently developing new therapies targeted to inhibiting gamma-secretase activity and screening drugs designed to do the job.

Dr. De Strooper’s accomplishments over the last decade have been frequently acknowledged. His honors include the Potamkin Prize, the Alois Alzheimer’s Award and the Pioneer Award from the Alzheimer’s Association. “I am quite optimistic about the possibilities of developing effective and safe secretase inhibiting therapies over the next 10 to 15 years, as well as learning more about how to help people live healthy, longer lives.”
In 1996, Robert Vassar was a post-doctoral fellow in Molecular Neuroscience at Columbia University studying olfaction when Amgen asked him to help expand their small neurosciences division by starting an Alzheimer’s group. At the time, Dr. Vassar’s mother was in her thirteenth year of decline due to the disease. He eagerly accepted the challenge.

When he joined Amgen, the cleavage of APP to form amyloid beta was well established. But little was known about the two enzymes doing the cleaving. Together with his collaborator, Dr. Martin Citron, Dr. Vassar and the Amgen team focused their attention on determining if inhibiting secretase activity could safely and effectively arrest the development of amyloid beta.

Between 1996 and 1999, Dr. Vassar and his team were the first to clone and characterize the beta-secretase enzyme, also known as BACE1. They then set out to validate that their BACE1 was the beta-secretase wreaking havoc in the brain. By creating mouse models without the gene for BACE1, Dr. Vassar demonstrated that the brains of such mice were free of the amyloid beta peptide. Furthermore, these mice appeared otherwise normal, with no obvious side effects from the absence of BACE1. These studies reinforced that BACE1 inhibition is a very promising target for Alzheimer’s treatment. The team’s 1999 publication of their findings in *Science* magazine intensified scientists’ investigations into beta-secretase and launched the quest for small molecule inhibitor drugs.

Dr. Vassar left Amgen in 2001 and is now Associate Professor of Cell and Molecular Biology at Northwestern University, where he has turned his attention to the dysregulation of BACE1 in Alzheimer’s and its relationship to levels of energy metabolism in the brain.

“I want to move upstream in the amyloid beta production process. I want to learn why BACE1 activity is being elevated in Alzheimer’s. I’m intrigued by the possible connection between an age-related reduction in energy metabolism in the brain and an increase in beta-secretase activity.”

Dr. Vassar’s latest work includes innovative explorations that could lead to gene therapy. He and his colleagues at Northwestern are looking at whether RNA-interference of BACE1 in adult mice can be used to reduce plaque levels. They have also shown that genetic deletion of BACE1 prevents amyloid beta-dependent memory deficits, brain cell loss, and plaques in mice. He is grateful for MetLife Foundation’s acknowledgement of the value of his contributions. “With NIH funding hard to come by, this award is coming at a critical time in our research.”
Professor, Departments of Pathology and Neuroscience
The Johns Hopkins University School of Medicine, Baltimore

As an assistant professor and researcher at Johns Hopkins University in the mid-1990s, Dr. Wong was both contributing to the discussion of gamma-secretase’s involvement in the formation of amyloid beta and listening closely to his peers. In 1997, Dr. Wong was among the first to publish findings indicating the central role of presenilin in the development and regulation of the communication pathway between brain cells, known as the Notch signaling pathway. Dr. Wong’s discovery that knocking out presenilin activity disrupts proper development of this pathway drove home the need for therapies that would be highly targeted to the specific enzymes involved in amyloid beta processing.

Dr. Wong was very quick to pick up on the significance of Dr. Robert Vassar’s work with beta-secretase, called BACE1. His team moved very quickly to develop mouse models with the BACE1 gene knocked out in an effort to validate this enzyme as an attractive therapeutic target for Alzheimer’s disease. Examining the neurons of his mice, Dr. Wong achieved this validation. He further demonstrated that while beta-secretase elimination could have adverse effects on a developing brain, these effects may not show up in a mature brain. Drs. Wong and Vassar’s back-to-back publications of their findings in a 2001 issue of Nature Neuroscience was a testament to the complementary nature of their work and led several pharmaceutical companies to start aggressive efforts to develop BACE1 inhibitors.

Having contributed to significant progress on BACE1, Dr. Wong turned his attention to the second cleaver in the amyloid beta production process, gamma-secretase. His interest in this enzyme was piqued by its complexity and its importance to proper development. For example, he observed that gamma-secretase deficiency can lead to skin tumors. Ongoing research on gamma-secretase has lead to the discovery that it is not a single protein enzyme but rather a series of enzyme complexes comprised of four different proteins. Dr. Wong’s discovery reinforced that blocking gamma-secretase activity as it applies to amyloid beta formation is still an attractive target for therapies, but to be effective and safe such drugs will have to target a specific sub-complex of the larger enzyme.

Dr. Wong’s latest work includes the development of methods delivering therapeutic drugs directly into the brain to avoid any side effects of treatment outside the brain. His work includes strategies to reduce the activities of both beta- and gamma-secretase.

“I envision treatment of AD requiring a cocktail of enzyme blockers,” he says, “much as has been used to treat patients with AIDS. We are at the dawn of a new era in the development of mechanism-based therapy for AD.”
Dr. David Holtzman and his team completed several landmark studies, each of which significantly advances our understanding of the biology of Alzheimer’s disease. First, the Holtzman lab uncovered a new set of mechanisms by which antibodies that bind to the soluble form of amyloid-beta found both in the brain and the blood can influence amyloid-beta toxicity in the brain. An antibody that rapidly binds to and detects transport of amyloid-beta out of the brain and into the blood was identified. This concept is now being tested in Alzheimer’s patients both diagnostically and therapeutically.

A second major accomplishment is in the search for biomarkers that indicate whether a person is developing amyloid plaques and will ultimately suffer dementia. His lab found characteristics in cerebrospinal fluid that correlate with the presence of amyloid in the brain. This finding could help identify healthy people who are candidates for therapies designed to prevent dementia before it starts.

A third area of discovery is the development of novel methods of dynamically assessing the formation and clearance of amyloid-beta in the central nervous system. His group’s development of a technique for assessing amyloid-beta levels in the brain on an hourly basis demonstrated that communication between nerve cells results in the release of amyloid-beta into the brain. The lab also developed a method of assessing amyloid-beta formation and clearance directly in the spinal fluid of humans. This technique allows researchers to determine if drugs currently in development are likely to work in humans.

Dr. Holtzman’s many honors include the Potamkin Prize from the American Academy of Neurology, the MERIT Award from the National Institute on Aging and the Zenith Award from the Alzheimer’s Association.

Every once in a while a scientist’s work fundamentally changes his peers’ views. Such is the case of the recent findings of Dr. Berislav Zlokovic.

Much of the work by Dr. Zlokovic, who is known internationally for his work on stroke as well as Alzheimer’s, focuses on the crucial role of blood vessels. He has shown that blood circulation and clearance at the blood-brain barrier play a key role in ridding the brain of the toxic amyloid beta that attacks the brains of Alzheimer’s patients.

His team has identified much of the molecular machinery that allows amyloid beta to sidestep the body’s safeguards and accumulate in the brain. As a result of this work, Dr. Zlokovic has suggested several strategies for preventing or lowering amyloid-beta accumulation by influencing the body’s ability both to clear it from the brain and to prevent its reentry from the blood stream. Dr. Zlokovic’s team has also discovered a link between vascular-restricted genes in brain capillaries and small brain arteries and dysfunction in the blood vessels of people with Alzheimer’s disease. When they restored the effects of these genes, they noticed growth of new blood vessels, reduction in the death of cells, improvement in the clearance of amyloid-beta at the blood-brain barrier, and improved blood flow responses to brain activation.

His recent accomplishments have earned him a MERIT Award from the National Institute on Aging, the Javits Award from the National Institute on Neurological Disorders and Stroke, awards from the National Heart, Lung and Blood Institute, and one of the inaugural ISOA/Elan awards for new drug discovery for Alzheimer’s disease.
During her career, Dr. Ashe has undertaken groundbreaking development of animal models for Alzheimer’s disease. Using mice engineered to produce human forms of beta-amyloid and tau proteins, Ashe has provided both the tools and the insights to further understand the role of these proteins in memory loss and neuron death. In 1998, the MetLife Foundation acknowledged Ashe’s early work with a Promising Work Award.

In 1996, Ashe and her colleagues announced the first mouse model of beta-amyloid plaque formation and memory loss. Since then, they have generously distributed the mice to other academic researchers without restriction, and the animals have been used in hundreds of studies.

More recently, Ashe focused her attention on the molecular basis for memory deficits, leading to the identification of small, soluble clumps of beta-amyloid that shut down normal memory function in mice without killing neurons. Likewise, Ashe’s work on the neurofibrillary tangle-forming tau protein points towards a reversible toxicity of individual or small clumps of tau peptides. The results are important because if reversible brain cell dysfunction accounts for memory loss in AD, then it should be possible to restore cell function and reverse cognitive decline.

“In our field, there was a decadelong heated debate about the role of amyloid versus tau. Now, that dispute has evaporated as we realize that they are both very important. Currently, the challenge is to integrate what we know of amyloid-beta and tau into a unified theory of Alzheimer’s disease,” Dr. Ashe said.

Toward that goal, Dr. Ashe welcomes the MetLife Foundation award and an opportunity to obtain equipment to streamline the genetic analysis of the mice used for her studies. “We screen 8,000 mice a year, and now we can automate that process,” she said. “That will move our program that much faster.”
In 2002, after a decadelong collaboration, Drs. Klunk and Mathis demonstrated that the deadly abnormal plaques of Alzheimer’s disease can be brought safely to light in the living brain. Their breakthrough marks a major turning point in efforts to test the efficacy of drugs designed to stop or reverse amyloid deposition in the living brain and to correlate diminished amyloid deposits with a decrease in the symptoms associated with the disease.

After testing hundreds of potential radiochemical PET tracers, Klunk and Mathis arrived at the thioflavin-T derivative now known as Pittsburgh Compound-B, or PIB. In mice, they showed that PIB entered the brain easily and bound tightly to amyloid proteins. The payoff for their painstaking work came when researchers in Sweden used PIB along with PET scanning to light up amyloid plaques in a patient with AD.

Klunk and Mathis are already applying their PIB-PET method to measure the effects of experimental treatments on amyloid load in Alzheimer’s patients, and their MetLife award will help that effort along. “Some of the MetLife funds will be used to support a project run by one of our junior investigators here in Pittsburgh looking at the effect of AN-1792 (the Alzheimer’s Vaccine) on amyloid load in AD subjects who participated in that trial,” said Dr. Klunk.

Since winning the MetLife Award, Klunk and Mathis received a MERIT award from the National Institute of Aging. These awards provide long-term grant support to investigators chosen by the NIH on the basis of their outstanding competence and productivity and their future promise. In addition, Dr. Klunk was named to the Medical and Scientific Advisory Council of the National Alzheimer’s Association.
John C. Morris, MD

John Morris has spent the last 20 years studying the changes in the brains of healthy aging people, people with mild cognitive impairment, or MCI, and people with Alzheimer’s disease. In 2001, Morris showed that senile plaques can appear many years, even decades, prior to any outward sign of abnormal brain function or dementia. By the time symptoms are recognizable, the disease process has already caused substantial damage to brain cells. His observation has led to the understanding that truly effective treatments for Alzheimer’s need to be introduced before symptoms appear.

To push back the clock on the diagnosis of Alzheimer’s disease to the earliest possible point, Morris has undertaken careful, long-term clinical studies searching for specific markers or traits that presage dementia. The scope and detail of Morris’ work have established a clinical diagnosis of MCI that reflects the dawn of symptoms of Alzheimer’s. His work identifying MCI has made possible a growing number of preventive, as opposed to purely treatment, trials for Alzheimer’s.

There remains a pressing need to go further, since even the limited symptoms of MCI may betray already irreversible brain damage, says Morris. “We are now studying people in their 40s who appear clinically normal, and are looking for changes in blood and cerebral spinal fluid biomarkers that might indicate disease even before MCI.”

Joining forces with fellow 2004 MetLife winners Klunk and Mathis, Morris and colleagues are also using noninvasive imaging techniques to seek out advance warning signs. Their first results, published last summer, pointed out new sites of interest for tracking brain damage in early Alzheimer’s.

Since receiving the MetLife award, Morris was honored with the 2005 Potamkin Prize (jointly with Ronald Petersen) from the American Academy of Neurology and the 2005 Physician-Scientist Lifetime Achievement Award from the Barnes Jewish Hospital (St. Louis) Foundation.
In 1999, Dr. Petersen gained significant attention when he published a report entitled *Mild Cognitive Impairment: Clinical Characterization and Outcome*. The study was among the first to show that patients who meet the criteria for MCI constitute a clinical group that can be characterized and targeted for early treatment interventions. Petersen went on to show that the patients with MCI progressed to AD at a much higher rate than the general population, suggesting that MCI could be distinguished as a unique clinical entity.

More than a decade of Petersen’s MCI research came to fruition in 2005 with the completion of the Alzheimer’s disease Cooperative Study’s three-year trial of Vitamin E and the widely-used AD drug donepezil for prevention of Alzheimer’s disease. In a high-profile publication in *The New England Journal of Medicine* in April, Petersen and colleagues reported that donepezil could delay the diagnosis of dementia by 12 months when it was given to patients with MCI. “The effect was modest but nonetheless this was the first study ever to demonstrate any ability to postpone the diagnosis of Alzheimer’s disease,” said Petersen. The landmark study establishes MCI as a critical point for early intervention in Alzheimer’s disease.

As the fourth Mayo Clinic researcher to capture the MetLife award, Petersen is using his research funds to expand collaborative programs in the outstanding research environment there. Specifically, he will invest in enlarging ongoing studies on using PET imaging to detect changes in the brain even earlier than MCI.

In 2005, Petersen was honored with the Potamkin Prize (jointly with John Morris) from the American Academy of Neurology. He was also the first recipient of the Ronald and Nancy Reagan Research Institute Award in 2004.
For the past decade, Dr. Roberto Malinow has focused his research on how activity in brain cells controls the strength of communication at the synapses between the cells. This process, called synaptic plasticity, is thought to underlie the formation and storage of memories. Malinow’s research has led to a greater understanding of how synapses form, as well as the role of amyloid-b peptides (viewed as central to the pathogenesis of Alzheimer’s disease) in normal synaptic activity and in disease.

“Most of our work has been addressing basic questions about how synapses work, how they get modified. From that beginning, we started to ask what things like Aβ do to the basic process,” Malinow said. In their very first studies, they came up with two novel findings. First, the researchers showed that increased neuronal activity causes increased processing of the amyloid precursor protein — when neurons fire more, they start making more Aβ. Then they discovered that the Aβ actually depressed synaptic transmission.

The work sheds a dramatic new light on the potential physiological role of Aβ in synapse function in both normal and diseased cells. Synaptic depression from excessive Aβ could contribute to cognitive decline during early Alzheimer’s disease. In addition, activity-dependent stimulation of Aβ production may normally participate in a feedback loop to keep neuronal activity in check. Disruption of this feedback system could contribute to disease progression in Alzheimer’s.

Now, Malinow is trying to understand the mechanism of how Amyloid beta affects synapses. He reports that they have interesting findings about how synapses get depressed, and how that can be prevented. “We’ve identified some mechanisms, processes and molecules, and when we do that, we see potential therapeutic targets,” Malinow said.

Dr. Thomas Südhof is a world leader in studies of how neurons communicate at synapses. For years he has led groundbreaking research on how presynaptic nerve terminals develop and function. Recently, Südhof’s lab turned its attention to studies of the role of amyloid precursor protein (APP) in synaptic activity. His studies led to a description of a novel function of APP in gene expression.

“The general consensus is that synapses may be the first to be affected by Alzheimer’s disease, and that symptoms are based on loss of synaptic function. But the issue is not settled, and I believe this is a pressing issue,” Südhof said.

Using an interdisciplinary approach that combines protein chemistry and molecular biology with mouse genetics and cell biology, Südhof’s studies have made fundamental contributions to understanding the normal function of APP. They serve as a basis for future studies of the underlying causes of Alzheimer’s disease. “The most important thing is to really understand the pathogenic process. There is evidence that Aβ peptides derived from APP are important pathological molecules, but this is not the whole story. We don’t know, and we need to know, how the brain becomes actually sick during the disease,” he said.

“In addition to feeling honored, the MetLife award encouraged me to deepen my interest in studying neurodegenerative disease,” Südhof said. The result has been a steady stream of publications from his team over the past few years on the newly-discovered gene regulatory role of APP. “The MetLife funds also motivated and supported additional studies on the pathogenesis of Parkinson’s disease,” he said.
Dr. Bruce Yankner has been conducting outstanding research in the field of neurodegenerative disease since 1987. The premise of Yankner’s work is that understanding the fundamental causes of neuronal degeneration and the role of the aging process is critical for treating and preventing Alzheimer’s disease. His research has led to many advances in the field.

In 1989, Yankner demonstrated for the first time that amyloid beta-protein is toxic to neurons. Later, his laboratory helped to establish how the amyloid β protein is produced and demonstrated a connection between presenilins in familial AD and the accumulation of this protein. His laboratory also provided some of the first insights into why neurons degenerate in Down’s syndrome, and developed a monkey model for studying Alzheimer’s disease.

Yankner’s research has repeatedly provided critical insights into promising therapeutic approaches. His work stimulated the development of strategies based on inhibiting the aggregation and toxic effects of the Ab protein, and also served as an impetus for a large-scale clinical trial of neuroprotective agents in young people with Down syndrome.

Despite these advances, Yankner says, “I recently became convinced that a major gap in our understanding of human neurodegenerative diseases is their relationship to normal brain aging.” When he turned his attention to a dissection of this problem, Yankner generated groundbreaking data showing that accumulated damage to brain DNA in humans results in aging-related changes in gene expression. “By these studies, we are attempting to obtain a greater understanding of the biology of normal human brain aging and how it interfaces with early Alzheimer’s disease,” he said. “We hope that this approach may lead to early prediction of individuals at risk and preventative intervention based on the molecular pathology of the aging process.”
Bradley Hyman, MD, PhD

Professor of Neurology, Department of Neurology/Alzheimer’s Research Massachusetts General Hospital and Harvard Medical School
Chief, Alzheimer Disease Research Unit Massachusetts General Hospital, Boston

Dr. Bradley Hyman’s career is focused on the study of Alzheimer’s disease with a goal of understanding the neuropathological and genetic factors that underlie dementia. His work has clarified the roles of the two major hallmarks of Alzheimer’s disease, demonstrating that neurofibrillary tangles are a proximate cause of neuronal loss and dysfunction, and amyloid plaque deposits are less directly correlated with neuronal loss or clinical symptoms. Another focus of Hyman’s lab has been the biology of ApoE, a genetic risk factor for Alzheimer’s disease.

Hyman’s most recent initiative has been the development of imaging techniques to observe plaques in living animals using multiphoton microscopy. This allows researchers to view with microscopic resolution neurons in an intact, functioning brain in mice, and track the pathological changes that occur during disease processes. An early and exciting application of the technology occurred when Hyman’s team showed for the first time that established plaques can be cleared by the therapeutic application of anti-amyloid antibodies. This work spurred the continuing efforts of researchers and companies to develop immunotherapies against the beta-amyloid-protein.

Multiphoton microscopy is proving to be an important tool in understanding plaque formation and for monitoring treatments designed to prevent or reduce their build up. Hyman used the MetLife award to push forward on imaging studies and develop genetically engineered mice complete with tagged proteins that illuminate neuronal activity in vivo. “With the extra funding, we’ve really been able to expand our multiphoton studies and take advantage of new gene transfer techniques to introduce fluorescent protein into mice,” Hyman said. “This has opened up a whole new avenue of experimental attack. I’m not sure we would have been able to take that risk without knowing that the MetLife support was there to help.”
Dr. Fred Gage received the MetLife award for his studies on the adult brain that uncovered an unexpected plasticity and adaptability throughout the life of all mammals. His work continues to offer new visions for replacing or enhancing the brain function lost due to Alzheimer’s and other neurodegenerative diseases.

Starting in 1995, Gage’s lab pursued research proving that, contrary to accepted dogma, human beings are capable of growing new nerve cells throughout life. His work established that small populations of immature nerve cells are constantly being born in the adult brain, and that these cells can grow up to become several kinds of brain cells, including neurons.

An important aspect of Gage’s current work is to understand how the neuronal stem cells he discovered can be prodded to mature into nerve cells to help repair brain damage.

In the 1990s, Gage and his colleagues showed that environmental enrichment and physical exercise enhanced the growth of new brain cells. They detected newly born neurons even in the oldest mice, and demonstrated that environmental enrichment can significantly increase the birth and survival of these new neurons. Recently, they expanded these studies by showing that exercise in older mice improves their learning and memory. These studies showed that voluntary exercise has a huge impact on brain function and structure, and provide unparalleled insight into the cognitive benefits of exercise.

Gage has pioneered other approaches harnessing the power of cells to repair the nervous system. One such method is the transplantation of genetically engineered cells made to produce neurotrophic factors or neurotransmitter. His current focus remains to understand the cell and molecular mechanisms for the birth of new neurons in the adult and aging brain and apply that knowledge to induce self-repair within the aged and damaged brain.
Dr. Dennis Dickson is recognized as an outstanding neuropathologist, especially as it relates to neurodegenerative disorders. The MetLife award acknowledges Dickson’s position as a key investigator of the relationship between amyloid deposits and neurofibrillary tangles in Alzheimer’s disease. Using antibody-based staining methods on human brains, he showed that some normal elderly individuals have as much amyloid in their brains as Alzheimer patients. They did not, however, have tau pathology as in Alzheimer’s disease. Working with his Mayo colleague and MetLife co-winner Michael Hutton, Dickson showed that some forms of frontotemporal dementia are caused by mutations in the tau gene. This added credence to the importance of tau in neurodegeneration.

The tau-amyloid controversy was recast by another Hutton-Dickson collaboration. Hutton’s group bred transgenic mice carrying the mutant tau gene and Dickson demonstrated that the mice developed neurofibrillary tangles composed of tau protein. When the team crossed the tau mice with animals that produce amyloid deposits, the offspring had amyloid plaques and showed enhanced neurofibrillary tangle formation, indicating for the first time an interaction between amyloid and tau.

Dickson currently oversees the neuropathologic characterization of postmortem brains from five different prospective, longitudinal research studies covering a variety of patient populations, including Parkinson’s disease.

Dr. Hutton is described by his peers as a “young investigator of the highest caliber.” He is one of the youngest scientists to receive the MetLife award, in recognition of his record of extremely important discoveries made in just a few years of independent research.

In 1998, Hutton marshaled an international consortium that cracked the genetic code of frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17). Hutton’s team demonstrated that the condition was caused by mutations in the tau gene. This discovery opened a new chapter in tau biology, emphasizing its importance in neurodegenerative disease, including Alzheimer’s disease.

Working from the tau mutations, Hutton has established valuable research models by introducing human tau variants into mice. Studies with his collaborator and co-winner Dennis Dickson established that the mouse model recapitulated human tangle pathology. Hutton’s more recent work has used these and other similar models to probe the mechanism of tangle formation and how this process leads to neurodegeneration.

One of the most valuable mouse models resulted when Hutton crossed the tau mice with mice that form amyloid deposits, generating a new line that developed both plaques and tangles. In the crossed mice, tangles began to appear in the cortex, demonstrating for the first time an interaction between amyloid and tau. Thanks to the work of Hutton’s team, scientists gained a research tool that closely approximates the dual plaque and tangle pathology of Alzheimer’s disease in humans.
Dr. Larry Squire is internationally known for his research into the neurological foundations of memory. His team has been among the leaders of the revolution in our understanding of what happens in the brain when we learn and remember. His team was the first to note that there are at least two forms of memory: procedural—which is concerned with habits, motor skills and perceptual strategies; and declarative—which is concerned with knowledge, or facts surrounding events. Their work has focused on the role of the hippocampus and surrounding cortex region of the brain in declarative human memory.

Others have shown that the earliest pathological changes in Alzheimer’s disease occur in the hippocampus and surrounding cortex, and studies like Dr. Squire’s explain why Alzheimer’s disease typically begins with memory impairment around facts and events. In addition, his work identifies the hippocampal system as an optimal target for early diagnosis of Alzheimer’s disease and the development of strategies for prevention and intervention.

“The MetLife Foundation’s award has allowed us to inaugurate new studies of how brain structures important for memory participate in the encoding, consolidation and retrieval of new information, and we are grateful for the flexibility and support that these funds have provided,” Squire said recently.

“Among our future hopes is work being planned with another Award recipient, Fred Gage, which aims to discover the function of the new neurons that are continuously being born in the dentate gyrus (an area important in memory that is compromised in Alzheimer’s disease). Understanding the function of these new neurons, and the broad purpose of neurogenesis, can guide the development of treatments for preserving healthy neurons and saving dying neurons,” he said.
Dr. Douglas Wallace was recognized by the MetLife Foundation for his pioneering research on the contribution of mitochondrial defects to neurodegenerative disease and Alzheimer’s.

The mitochondrion is the energy-producing machine of the cell, and there is growing evidence that defective mitochondrial bioenergetics are a major contributor to the pathology of degenerative brain disorders such as Alzheimer’s disease. Wallace has been a world leader in the study of human mitochondrial genetics for many years, and his work has led to the idea that mutations in mitochondrial DNA might be important for aging. He also showed that such changes could be measured in several neurodegenerative diseases. Recently, Wallace and his colleagues have shown specifically that Alzheimer’s patients carry deleterious mutations of important control regions in mitochondrial DNA that are not present in normal aging people.

Wallace’s work suggests a possible unifying hypothesis of aging and degenerative diseases that places mitochondria at the interface of genes and the environment. Since brain cells are highly dependent on a good energy supply, the brain may be the organ most susceptible to genetically-influenced deficiencies in mitochondrial function. The mitochondria are also the source of damaging oxygen free radicals, and any genetic defects or environmental insults that increase the production of radicals could induce the mitochondria to trigger the destruction of the cell by apoptosis. While this idea is gaining currency as our understanding of aging advances, Wallace remembers that back in 1999 it was not as well known. “The MetLife Foundation’s recognition was very important to me because it was the first official statement that our studies on mitochondrial dysfunction could be important in Alzheimer’s disease,” he said recently. “For this, I am very grateful.”
Dr. Paul Greengard has spent nearly 50 years attempting to determine how the brain’s chemical messengers produce their effects on nerve cells. In the process, he has transformed molecular neuroscience, making a profound and continuing impact on the field of Alzheimer’s disease research. After winning the MetLife award, Greengard went on to capture the Nobel Prize for Physiology or Medicine in 2000. His research has continued apace, and in the past year he published two major findings related to Alzheimer’s.

Greengard is the world’s leading contributor to our understanding of protein phosphorylation in the nervous system. Greengard has shown that phosphorylation — the process by which a phosphate molecule is either added to or removed from a protein — regulates the extent to which amyloid precursor protein, or APP, is converted into the toxic b-amyloid protein. Recently, he and his colleagues discovered that inhibiting phosphorylation with a drug commonly used for the treatment of cancer can lower levels of b-amyloid in brain of experimental animals. This work could provide a fast track to Abeta-lowering therapy for people.

Greengard’s recent work also yielded another important insight into how b-amyloid might destroy the synaptic connections between neurons. A recently published study shows that b-amyloid, by binding to a receptor on nerve cells, sets off a signaling pathway that ends with in the disappearance of key neurotransmitter receptors from the synapse. These results provide a mechanism for the synaptic dysfunction that characterizes AD, and the pathway offers several potential targets for therapeutic intervention.

“The progress in terms of AD research in the past 20 years has been enormous,” Greengard said recently. “Nearly everything we know has been discovered in the last 20 years.” While we still face some unsolved mysteries, says Greengard, “At least now we can formulate specific questions, which was not possible before.”
When he began a stint in Donald Price’s lab in 1988, Dr. Sangram Sisodia confesses, he didn’t know what a neuron was. “I was a pure-bred molecular biologist,” he recalled. But he quickly combined his expertise with Price’s grounding in pathology to make important discoveries about how the amyloid-b precursor protein (APP) is processed and transported in the brain. Later, in his own lab, he revealed key knowledge about the presenilins, APP-processing enzymes which are mutated in the majority of cases of early-onset familial Alzheimer’s disease.

Sisodia’s demonstration presenilin mutations changed APP processing to elevate the formation of toxic Ab42 peptides provided an important convergence point between the deposition of disease-related amyloid and the signaling pathway of the presenilin proteins. This work spurred research by several large pharmaceutical companies to discover inhibitors of the gamma-secretase activity of presenilins, with the result that drug candidates are now in early-stage clinical trials in humans.

One of Sisodia’s outstanding contributions is the introduction of the human APP gene and presenilin proteins into mice. His animal models provided the first opportunity to witness in living organisms processes that had previously only been studied in test tubes. The AD mice have proven invaluable for exploring the mechanisms of disease progression, and testing potential therapies. Recently, Sisodia and his colleagues showed that exercise, an intervention that seems to lower risk of AD in humans, decreased amyloid deposition in AD mice. In this case, Sisodia’s mice will allow researchers to probe not just the genetic factors, but also important environmental factors that contribute to Alzheimer’s.

As a result of his contributions, Sisodia is regarded as one of the outstanding molecular biologists investigating the pathogenesis of Alzheimer’s disease. His international reputation for keen insight, objectivity and the elegance of his scientific methods have been recognized with numerous awards for his work.

Dr. Steven Younkin’s research has uncovered how mutations that cause familial forms of Alzheimer’s disease modify the cellular processing of the amyloid-b (Aβ) protein. In particular, he has shown that mutations in the amyloid precursor protein (APP) as well as the presenilins have a common effect of increasing the concentration of a particular form of Aβ, called Ab42, which is deposited selectively in the AD brain. These results set off a gold rush as most major pharmaceutical companies began to prospect for compounds that could specifically shut down Ab42. The result has been extensive preclinical work and clinical trials (up to Phase II so far) of new therapies for AD.

Today, Younkin is focused on understanding the complex genetics of AD, a difficult problem he thinks will be cracked within the next decade. By then, he says, there is a good chance that we will have cataloged the complete set of gene variants that affect the occurrence of AD. This knowledge will be helpful to predict individual risk and identify people who will benefit from early therapy.

“Everyone agrees that therapy will be best if given in preventive mode,” Younkin says. “The idea is to identify those at immediate risk and treat them before difficulties develop.” As one way to do this, Younkin and his collaborators are now working on a blood test that uses the ratio Ab42 to the normal Ab40 as a predictor of who will get AD.

Dr. Younkin’s contributions have been recognized with many awards and honors. As Director of Research at the Mayo Clinic in Jacksonville, he oversees a team of 90 scientists and support staff (including two other MetLife award winners) whose research is focused exclusively on Alzheimer’s disease and other degenerative brain disorders.
Dr. Yasuo Ihara is regarded by many as the leading researcher on Alzheimer’s disease in Japan. Students and research fellows interested in the disease seek out Dr. Ihara and his institute, where he has spent over two decades studying Alzheimer’s disease.

Ihara received the MetLife award for his work on the purification and analysis of the paired helical filaments found in the brains of Alzheimer’s disease victims. Though several groups were honored for their contributions to the understanding of the structure and composition of the PHF, Ihara has a well-deserved reputation for providing the most direct and rigorous protein chemical analysis available.

Ihara and his colleagues provided the seminal biochemical data that the abnormal tau protein is the principal constituent of PHF. Ihara’s group also made the important discovery that amyloid plaques in humans are made mainly of Ab42 peptide, despite the fact that Ab40 is the major peptide secreted by cells. Ihara and his colleagues continue to contribute to our understanding of the intramembrane processing of the amyloid precursor protein by g-secretase, as well as the pathways of tangle formation and neuronal death involving tau protein and paired helical filaments.

“The award from MetLife as well as the 1995 Potamkin Prize was a great honor to me, as my work was judged by a committee of my international colleagues outside Japan to be worthy of such an award,” Ihara said recently.

Now Ihara and his researchers have turned to a novel model organism, the roundworm C. elegans, to understand how tau kills neurons. They showed that introducing mutated tau into the worm’s neurons triggers age-related neurodegeneration. Ihara is now undertaking a large-scale gene expression analysis to find any abnormally active or inactive genes which may be involved in tau-mediated neuronal degeneration.
Drs. Lee and Trojanowski received the 1996 MetLife Award in recognition of their singular contributions to research on the pathogenesis of Alzheimer’s disease and a number of AD-like dementias of the elderly. The award followed their recognition as promising young investigators by the MetLife Foundation in 1991.

Trojanowski and Lee’s work over the years preceding their award elucidated the biology and function of the tau proteins, the building blocks of AD neurofibrillary tangles (NFTs). In 1998–99, after the role of tau in neurodegeneration had been neglected by most in the field for many years, tau gained its own spotlight when Trojanowski, Lee and others showed that mutations in the tau gene cause hereditary AD-like disorders, and that tau transgenic mice developed a neurodegenerative disease. Since then, the researchers have conducted further studies on neurodegenerative tauopathies and on additional transgenic mouse models of tauopathy all of which have proven invaluable in understanding the role of this protein in mechanisms of neurodegeneration in AD and related tauopathies. For example, tau pathologies lead to defects in axonal transport, and Lee and Trojanowski’s recent work shows that microtubule binding drugs like the anti-cancer agent Taxol can reverse neuropathology in a tau transgenic mouse model of AD-like neurodegeneration.

Their program today focuses on the pathobiology of tau, b-amyloid and synuclein, three proteins that form filamentous lesions in neurodegenerative diseases. Moreover, since observing years ago that an increase in tau protein in cerebrospinal fluid might reflect the presence of AD during life, Lee and Trojanowski have continued to pursue efforts to develop biomarkers of AD. Since interest in diagnostic markers has mushroomed now, the work of Trojanowski and Lee set the stage for Penn to be the site of a biomarker discovery effort involving a multicenter initiative to develop simple tests for early biomarkers of AD. The effort, known as the Alzheimer’s Disease Neuroimaging Initiative, or ADNI, which is funded jointly by the NIH and pharmaceutical companies, will span the next five years, and if successful, will open up a window of opportunity for truly effective early treatment by providing standardized and informative biomarker assays for the early diagnosis of AD and for monitoring potential new therapies to treat this disorder in clinical trials.
Dr. Brenda Milner’s work in the field of neuropsychology spans five decades. Neuropsychology bridges studies of the brain and behavior, and is an integral part of modern cognitive neuroscience. Milner’s research on the processes of human memory began in the 1950s with a series of studies on one patient with bilateral damage to the medial structures of the temporal lobe. The patient (HM) had a profound loss of some types of memory, the first indication that memory is not a single brain system.

Milner’s continued observations on patients with temporal lobe lesions established much of our present understanding of the brain circuitry underlying memory processes. “When I got the MetLife award, I thought they’d made a mistake,” Milner recalled. “I don’t work on Alzheimer’s disease, I work on memory.” But the foundation recognized that Milner’s pioneering work is directly relevant to the study of Alzheimer’s, where medial temporal-lobe pathology and memory loss occur early and are a hallmark of the disease.

As newer techniques like PET imaging and MRI have come on line, Milner has been able to combine precise anatomical and functional measures with her other analyses to gain more insight into memory functions. Now in her 80s, Milner continues to run an active research program.

Though best known for her work on memory, Milner has also made significant contributions to our broader understanding of the behavioral mechanisms of the brain. Specifically, she has contributed greatly to the study of hemispheric specialization, the effects of early brain damage on cerebral organization at maturity, and the cognitive functions of the frontal lobes. In recent years she has expanded the scope of her work to include the exploration of brain regions involved in the performance of specific linguistic and mnemonic tasks.
For two decades, Drs. Thomas Bird, Gerard Schellenberg and Ellen Wijsman have jointly led a research initiative that has resulted in discoveries on the genetics of inherited Alzheimer’s disease.

In 1988, the Seattle team demonstrated that the type of Alzheimer’s affecting some families was not related to the amyloid precursor gene on chromosome 21 and, therefore, not related to the parallel pathology observed in Down syndrome. This was the first definitive evidence that various forms of Alzheimer’s disease have different genetic origins and clearly established the role of genetic heterogeneity in Familial Alzheimer’s disease (FAD).

Over the next several years, the group performed an exhaustive search for genes responsible for early-onset Alzheimer’s in these new families. In 1992, their search resulted in the first identification and mapping of a region on chromosome 14 containing a gene responsible for early-onset Alzheimer’s disease. That gene turned out to be presenilin 1, now known to cleave the amyloid precursor protein to release the amyloid-beta peptide. This group then located another Alzheimer region on chromosome 1 that proved to be presenilin 2. In 1998 they were one of the first groups to identify mutations in the tau gene causing familial frontotemporal dementia. Since then, the trio has focused on identifying novel genes that govern susceptibility to late-onset Alzheimer’s disease. They reported success last year finding a new chromosomal locus for late onset familial Alzheimer’s disease on chromosome 19, and have recently developed super-sensitive statistical methods to look for additional linkages.

“This has been a very good collaboration,” Wijsman said of her work with Bird, a clinical neurologist and Schellenberg, a molecular geneticist. “These are not single person projects, and we are grateful to the MetLife foundation for recognizing that it takes a group effort to make progress against a tough disease like Alzheimer’s.”
Dr. Tanzi received the MetLife Award for his isolation of the amyloid precursor protein (APP) gene, and his significant contributions to the identification and characterization of the presenilin genes. His lab continues to be in the forefront of the analysis of the mutations in these genes and their molecular and biochemical byproducts.

Cloning of APP began a new era in AD research, but there are still many genes to discover, Tanzi says, especially in the case of late-onset disease. “The cause of 70 percent of familial Alzheimer’s disease is unsolved by the known genes,” he explained. “If we can identify all the other genes, each gives a new window into understanding the disease. And when you know a particular gene is involved, then you may have a useful target for therapeutics.” Tanzi and his collaborators recently identified one of those genes, ubiquilin 1, on chromosome 9, and showed it is involved in helping neurons dispose of abnormal proteins.

To help speed the pace of untangling the complicated genetics of AD, Tanzi has worked with colleague Lars Bertram to establish a comprehensive database (Alzgene) of all published studies looking for genes associated with AD. By pooling data for meta-analysis, Tanzi and Bertram can make the most of the available findings, and post scorecards tallying the relative contribution of each gene to the disease risk on their freely accessible Web site. Founded just a year ago, the Web site now encompasses data from nearly 700 scientific publications on over 200 different genes. “We need this kind of analysis for all genetically complex diseases, and we are happy to be able to provide this service for the field,” Tanzi said.

In addition to investigating the biochemical mechanisms by which defects in the known AD genes cause disease, Tanzi has also contributed to the identification of genes for other neurological diseases.
From 1987–92, Drs. John Hardy and Alison Goate co-led a research group studying the genetics of Alzheimer’s disease at St. Mary’s Hospital Medical School in London. They received the MetLife award for their 1991 demonstration that a mutation of the β-amyloid precursor protein causes an inherited form of early-onset familial Alzheimer’s disease (FAD). This achievement has focused research on the amyloid cascade hypothesis, and many of the advances of the past fifteen years have flowed from their discovery.

“The biggest reward for me would be to see a therapy based on the amyloid cascade hypothesis,” Hardy said recently. “My hope is that we will see that come to fruition in the next decade.”

The smooth teamwork of Hardy and Goate continued after they had both left St. Mary’s, and in 1995 their labs reported the full structure of presenilin 1, the second Alzheimer’s gene. Hardy and Goate credit the MetLife funds for getting that effort off the ground. “Basically, we could not have done our presenilin work without the MetLife award money,” Hardy said. “My university matched the funds, and we used it to put together a sequencing facility, which allowed us to be competitive for the next stage of our research.”

Since then, both researchers were involved in showing that mutations in tau, a component of neurofibrillary tangles, also can cause dementia in humans. Hardy and Goate continue to collaborate, now searching for genes that increase the risk of late-onset, sporadic Alzheimer’s disease, which accounts for the vast majority today’s cases. Recently, they reported evidence for a new susceptibility locus on chromosome 10, and hope to be zeroing in on yet another pathologic gene soon.
Dr. Robert Mahley and Dr. Karl Weisgraber have been collaborating on the study of plasma lipoproteins since 1972. Together they identified critical changes in lipoproteins associated with the development of accelerated atherosclerosis caused by dietary fat and cholesterol. They demonstrated that these diet-induced lipoproteins were highly enriched in a new protein that was apolipoprotein (apoE).

By the 1980s, Mahley and Weisgraber had already demonstrated that apoE affects the growth of nerve cells, sparking interest in the role of apoE in the brain. Their early characterization of the structure and function of the apoE isoforms E2, E3 and E4, laid the groundwork for an explosion of research after 1993, when the involvement of apoE4 in Alzheimer’s disease was first recognized.

The researchers used their MetLife prize funds to advance their basic understanding of apoE4 function in the brain. “We were able to accelerate the planning for the production of transgenic mice expressing apoE3 and apoE4 in the central nervous system. These studies ultimately established that overexpression of apoE4 leads to neuropathological changes in the brain of the mice and impaired learning and memory. ApoE3 expression did not result in detrimental effects and was in fact protective against the effects of aging and the administration of neurotoxins. These animals continue to be important animal models for the study of apoE and Alzheimer’s disease,” Mahley said.

From these studies, and others, Mahley and Weisgraber have come to believe that apoE4 harms neurons via multiple distinct pathways, only some involving β-amyloid directly, and all of which may be involved in multiple neurodegenerative diseases. Their latest findings suggest that apoE is produced during injury or disease to protect neurons, but apoE4, with its unique structure, may act perversely to cause further damage. They continue to search for ways to modify apoE4’s structure and function as a new therapeutic approach to Alzheimer’s disease.
Blas Frangione, MD, PhD

**Professor of Pathology and Psychiatry**  
**Head, Division of Alzheimer’s Disease Research**  
**New York University Medical Center**

Dr. Frangione, an immunologist turned neurobiologist, conducted many of the earliest studies on amyloid proteins and their roles in disease and aging. Amyloid proteins of all types are insoluble and difficult to isolate and study. In 1982, Frangione developed a method for extracting insoluble cerebral amyloid from leptomeninges of brain tissue. “This was not a little thing,” Frangione said recently. “For 75 years biochemists had been unable to extract amyloid from the brain. Alzheimer knew it was there, but he couldn’t extract it.” Two years later, George Glenner used Frangione’s method to successfully isolate and identify the Alzheimer’s amyloid.

Frangione also gets credited with discovering the first disease-causing mutation of the Alzheimer’s amyloid precursor protein (APP), in a Dutch family where deposition of amyloid in the blood vessels of the brain caused early strokes. This work provided an enormous stimulus to look for mutations in other Aβ amyloidoses, including Alzheimer’s disease, and the first familial AD gene was uncovered shortly after.

Work from Frangione’s laboratory and collaborators produced other firsts: the first evidence that apolipoprotein E (apoE) participated in amyloid formation in brain, and the first trace of a soluble form of Ab that circulated freely throughout the body. Most recently, Frangione’s team discovered a new type of amyloidosis that includes neurodegeneration and dementia, caused by a novel gene they found mutated in two families.

Frangione’s work on soluble amyloid laid the foundation for current efforts to establish the measurement of this protein in blood or cerebrospinal fluid as a diagnostic biomarker for AD. In the treatment arena, he and his colleagues have developed small, peptide-like compounds that interfere with Ab aggregation. Such b-breakers, as Frangione calls them, could offer a more generalized treatment for amyloid diseases, which all involve pathogenic protein clumping, he said.

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Allen D. Roses, MD

**Jefferson-Pilot Professor of Neurobiology and Genetics, Professor of Medicine (Neurology)**  
**Director, Deane Drug Discovery Institute, R. David Thomas Center, Duke University, Durham, North Carolina**

Dr. Roses was one of the first clinical neurologists to apply molecular genetic strategies to identifying the genes that contribute to neurological diseases. In 1993, Roses discovered that apolipoprotein E4 (apoE4) is a susceptibility gene for Alzheimer’s disease. By analyzing late-onset Alzheimer’s disease in families, Roses and his colleagues found a region on a chromosome 19 that was associated with elevated risk of AD. In separate experiments they discovered the apoE protein bound to β-amyloid. Knowing that the apoE gene was on chromosome 19, Roses rushed to genotype a number of patients to check for the presence of different apo gene forms. The results, Roses said, were astounding. “Normally, one third of people carry one or two copies of E4. In our Alzheimer disease patients, 60 percent carried it.”

In subsequent studies, Roses and his colleagues showed that the apoE4 gene increased disease risk and lowered the age of onset in an inherited dose dependent manner, while apoE2 had the opposite effect. Today, the apoE4 allele is still by far the strongest genetic risk factor known for sporadic AD, the type that affects most people. Roses’ genetic insights will have a major impact on future epidemiological studies, drug treatment protocols, and diagnostic/prognostic testing strategies.

Roses has received many awards for his work, and in 1997 he made an unorthodox career move by leaving his successful academic life to join a pharmaceutical company as head of their genetics program. “After we identified the gene, I decided to go to a drug company with the hopes of turning that discovery into an Alzheimer’s drug,” Roses said. His studies on the metabolic pathways that are impacted by apoE4 have led to clinical testing of an FDA-approved diabetes drug for Alzheimer disease. Early results from human testing are expected this year.
Dr. Prusiner has made a series of fundamental contributions to understanding basic mechanisms of neurodegeneration. Based on pioneering studies of transmissible degenerative brain diseases, in 1982 he proposed the existence of a completely new type of disease-causing particle. Different from viruses or microbes, the particle contained only protein, and Prusiner dubbed his new agents prions, for proteinaceous infectious particles. Despite an immediate storm of resistance from infectious disease researchers, Prusiner persevered and by the time he was awarded the MetLife prize in 1991, the idea of prion protein-caused disease was gradually gaining acceptance.

The sheep disease scrapie and its human counterparts Creutzfeld-Jakob disease and kuru, arise when prions induce normal brain proteins to misfold into a pathological shape, and form cerebral amyloid. Since Prusiner’s first discoveries, other researches have found misfolding and aggregation of proteins to be a common theme in many neurodegenerative diseases. In Alzheimer’s disease, it is amyloid-b peptide aggregates that disrupt neuronal function and deposit as plaques.

Prusiner’s current research is focused on dissecting the molecular events that occur as a new prion is formed, and also on finding ways to prevent prion diseases. “My colleagues and I continue to search for effective therapeutics that can be used to treat people dying of prion disease. I am hopeful that such therapeutics might also find application in the treatment of Alzheimer’s, Parkinson’s and Huntington’s disease,” he said recently.

For his trailblazing research, Prusiner received many awards, including the 1997 Nobel Prize in Physiology or Medicine.
Dr. Terry has the distinction of receiving the first grant ever given by the NIH to study Alzheimer’s disease. That funding, in 1960, supported electron microscopic studies of brain biopsies from which Terry described the ultrastructure of the tangle and the plaque in essentially all the details that have been reported to date. He also studied plaques in aged dogs and monkeys, and assayed neuronal populations in both normal aging and in Alzheimer’s disease. Later, Terry worked with Eliezer Masliah to develop techniques for quantifying synaptic density in human brain tissue. They showed synaptic density strongly correlated with the mental status in Alzheimer’s disease to the extent that many now believe that synaptic loss is the cause of cognitive deficiency in AD.

A true leader, Terry started his research when no one else was working on Alzheimer’s disease. “Research on dementia is now a worldwide industry, and it has been wonderfully exciting and satisfying to see the progress,” he said recently. “Pathologists are by training reluctant to predict the future, but it is obvious that real progress is being made in research and treatment of Alzheimer disease. Recognition of the very earliest stages of the disease is improving by several means. That is very important because no treatment will restore the brain once the disease is apparent, so it must be recognized and arrested before it starts.”

Dr. Terry began his professional career at Montefiore Hospital and Medical Center in New York. He has been affiliated with many institutions, including the Albert Einstein College of Medicine, the Institut de Recherches sur le Cancer in Paris, and the Institute of Neurology at the National Hospital in London, and has been the recipient of many awards for his work. After more than 40 years in the field, Terry remains active and continues to publish.
Dr. Price, a neurologist-neuropathologist-neurobiologist, has wielded diverse research tools to make important contributions to understanding Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), and other neurodegenerative illnesses. His work of the past two decades underlies many of the therapeutic approaches currently in the clinic or in development for AD.

In 1981, Price and colleagues demonstrated that many patients with AD show abnormalities in cholinergic neurons in the basal forebrain. Subsequently, they elucidated the consequences of damaging the cells and the roles of neurotrophic growth factors in maintaining these neurons. Now, cholinesterase inhibitors and other cholinomimetics are commonly used to treat symptoms of AD, and growth factors continue to interest clinicians.

Using funds from his MetLife award, Price recruited a cohort of outstanding young basic scientists to undertake some of the first molecular and biochemical studies of amyloid protein processing and to create transgenic models of diseases. Their work was so productive, Price was ranked by Science Watch as one of the top ten neuroscientists during the “Decade of the Brain” (1990–2000), because of the number of highly cited papers he published during those years.

During that time, Price and colleagues used genetically engineered mice to demonstrate that the β-secretase is BACE1 and that PS, Nct, and Aph-1 are major components of β-secretase; all of these proteins are critical for generation of toxic amyloid peptides by neurons and are now recognized as therapeutic targets by multiple pharmaceutical companies trying to develop secretase inhibitors. Moreover, the transgenic mice they created as model systems for neurodegenerative diseases including AD, ALS and Parkinson disease, have turned out to be invaluable for investigating disease mechanisms and for testing novel therapies leading to clinical trials.

Price now serves on the MetLife Foundation Advisory Committee.
George G. Glenner, MD

Research Pathologist
School of Medicine
University of California, San Diego
(Deceased 1994)

A graduate of the Johns Hopkins University School of Medicine, Dr. Glenner was Chief of the Section on Molecular Pathology at the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health for 26 years before he went to the University of California, San Diego, where he established the world’s first tissue/brain bank for Alzheimer’s disease diagnosis and research.

In 1970, Glenner discovered the pathogenic action of a protein composing the abnormal silk-like fibrils in systemic amyloidosis, a lethal disease. These amyloid fibrils are similar in structure to those seen in the brain in Alzheimer’s disease, and in 1984 Glenner was the first to discover the amyloid beta protein in the brain tissues of people with AD and Down’s syndrome.

He predicted the gene coding for this protein would be found on chromosome 21, a prediction later confirmed.

“George Glenner was a real pioneer who discovered the amyloid protein. He was a father figure in the amyloid field,” said Dennis Selkoe, who won the first annual MetLife Award in 1986 for his own studies of amyloid in Alzheimer’s disease.

Glenner was also the founder and president of three nonprofit Alzheimer’s Family Day Centers in San Diego County, Chairman of the California State Alzheimer’s Disease Task Force and Director of the National Brain Bank. In 1988, he was given the Potamkin Prize for Alzheimer’s disease Research, a Merit Award for ten years of research support by the National Advisory Council on Aging, and in 1991, the Paul F. Glenn Award by the Gerontological Society of America.

Alzheimer’s Amyloid

1988

Carl W. Cotman, PhD

Professor of Neurology and Behavior
Director, Institute for Brain Aging and Dementia
University of California, Irvine

Dr. Cotman’s research has concentrated on the study of synapses, their basic properties, plasticity and ability to participate in the restoration of function. The brain’s ability to heal itself is one of the novel concepts supported by Cotman’s research, a concept that has opened up new approaches in Alzheimer’s research.

Cotman is a leader in seeking ways to improve brain function in the elderly and prevent degeneration. He was one of the first researchers to study the potential for physical exercise to impact brain function. In the early 90s, he and his colleagues demonstrated that running induced neurotrophic factors in the brain in rodents. Recently, he extended this work to Alzheimer’s disease, and showed that voluntary activity reduced amyloid and improved learning in a transgenic mouse model. Cotman also established a novel model of Alzheimer’s in beagles, showing that these animals naturally deposit amyloid and develop learning deficits with age. In the dogs, he showed the positive effects of exercise and a diet rich in antioxidants on aging and plaque deposition.

A direct result of Dr. Cotman’s work and enthusiasm has been his establishment of a comprehensive research and assessment clinic for Alzheimer’s victims on the UC Irvine campus. The clinic provides thorough tracking of the disease’s progress using techniques ranging from short-term memory tests to biochemical markers of the disease.

“As I remember, the MetLife funds helped get me started on some of our more novel work on how exercise affects the brain,” Cotman said. “Now a lot of this work is being translated into strategies to delay onset and improve function in humans, and that is very exciting.”

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Dr. Gusella reported the first major success in pinpointing the location of a DNA marker for an unmapped genetic disease in 1983. His work, which led to the identification of the gene responsible for Huntington’s disease, opened up myriad possibilities for researchers studying inherited disorders, including Familial Alzheimer’s disease.

The MetLife award permitted Gusella to continue different molecular genetic studies of Alzheimer’s disease with his trainee and co-winner, Peter St. George-Hyslop. The funds also supported Rudy Tanzi, who went on to win the MetLife award in his own right in 1995. “I eventually ceded the AD field to Peter and Rudy, as they emerged as independent investigators, while my own lab then focused on the longstanding search for the Huntington’s disease gene and genetic studies in other neurogenetic disorders,” Gusella said.

Gusella’s work helped to establish the paradigm of a genetic research cycle, which begins with a patient population and definition of phenotype. Then, researchers use that phenotype in genetic studies to identify a disease or modifier gene, followed by investigations of how the gene causes disease using molecular genetics and model systems. That information is then used to improve diagnosis, management and treatment, completing the cycle by returning benefit to the patient population.

As director of the Center for Human Genetic Research (CHGR) at the Massachusetts General Hospital, Gusella oversees a multidisciplinary, cross-departmental group of researchers who are applying this paradigm to all areas of medicine. In the future, he sees researchers identifying more susceptibility and disease modifier genes for AD, followed by targeted drug screening and testing, first in animals and then in humans. His own work continues to focus on related areas of Huntington’s disease, Parkinson disease, and other neurological disorders, for which he has received numerous awards.

Dr. Peter St. George-Hyslop was given the MetLife award for work he did with co-winner James Gusella at Harvard University that gave the first definitive lead to finding a gene for familial Alzheimer’s disease on chromosome 21. That gene was later identified to be the amyloid precursor protein. Subsequently, St. George-Hyslop mapped and cloned four more genes associated with AD, and continues to work on additional candidates.

Early on, St. George-Hyslop used molecular genetic strategies to resolve a longstanding controversy as to whether Alzheimer’s disease was a single homogeneous disorder or a group of disorders with different causes but similar clinical and pathological features. The results of this international collaborative study, which was supported in part by the Metropolitan Life Foundation Award, clearly showed that Alzheimer’s disease is not a single disorder, but rather has a number of different genetic and non-genetic etiologies.

Using funding from the MetLife award, St. George-Hyslop cloned both of the presenlin genes, which he showed had missense mutations in a small number of FAD cases. Both proteins encode enzymes that process APP into Ab, and part of St. George-Hyslop’s current work focuses on understanding how the presenlins and their protein partners form the novel protein-processing complexes used for many important cell functions. Analysis of the presenilin complexes and their components provides clues to their function, as well as potential therapeutics for Alzheimer’s disease.

St. George-Hyslop has been recognized with numerous awards, and is an international research scholar of the Howard Hughes Medical Institute.
Peter Davies, PhD

Judith and Burton P. Resnick Professor of Alzheimer’s Disease Research
Professor of Pathology and Neuroscience
Albert Einstein College of Medicine of Yeshiva University, New York

Dr. Davies was awarded the first MetLife Foundation Award for Medical Research for his work in establishing a neurochemical basis for Alzheimer’s disease (AD). Davies’ early work helped to demonstrate the deficiency of acetyl choline in the brains of patients with Alzheimer’s disease, and his work formed the basis for the current use of drugs such as Aricept and Cognex to treat the symptoms of AD.

After 1986, Davies initiated some of the earliest studies on the production and use of monoclonal antibodies to study protein abnormalities in the brains of patients with Alzheimer’s disease. These antibodies have been supplied to numerous other research groups around the world. “The work we did with funding from MetLife allowed us to open new areas of research, which continue today,” Davies said. Some of that work led directly to his 1989 MERIT award, a coveted ten-year research grant given by the NIH to only to the most highly productive researchers.

Since then, Davies has continued his work in trying to define the sequence of biochemical events that occurs as Alzheimer’s disease develops, and in trying to develop new strategies for the discovery of treatments for the disease. Today, he said, the Alzheimer field is in transition. “We have spent about 30 years investigating pieces of the puzzle — tau, amyloid, ApoE, et cetera, and I think we now have enough pieces of the puzzle to begin to try to put them all together. This is a real change. I’m not just looking at one piece of the puzzle, I’m really trying to put the whole thing together,” Davies explained. “It’s a fun time to be in the field.”

In 2003, in recognition of his continued outstanding contributions to research, Davies received a second MERIT award.

Dennis J. Selkoe, MD

Vincent and Stella Coates Professor of Neurologic Diseases
Harvard Medical School Co-Director, Center for Neurologic Diseases
Brigham and Women’s Hospital, Boston

Dr. Selkoe received the first MetLife Foundation Award twenty years ago for his groundbreaking studies of the biochemistry of the neurofibrillary tangles and amyloid plaques that characterize Alzheimer’s disease. Recognized for his original work that established the “amyloid hypothesis” of AD, Selkoe and his colleagues have since uncovered much of what we now know about the origins and behavior of toxic amyloid-b (Ab) protein in the brain.

Selkoe’s impact on the field has been enormous, and his work has garnered numerous additional prizes. But receiving the MetLife Award, his first major recognition for Alzheimer’s disease research, was a defining moment in his career. “This honor was a real shot in the arm at a critical time when I was just starting to focus on the amyloid problem,” Selkoe said recently.

Pushing ahead, he invested the award funds in developing his lab and hiring young researchers to pursue biochemical investigations of amyloid proteins, an effort that continues today. From showing that inherited forms of AD stem from overproduction of Ab, to identifying presenilin as the active core of the Ab-generating g-secretase complex, to their most recent work on the g-secretase structure, the Selkoe lab has routinely turned up discoveries that are now being translated into promising new therapies.

What excites Selkoe most these days are the preliminary indications that Ab-lowering treatments may work in the clinic. “After 20 years, I wish we would be further along,” Selkoe admitted, “but the message is, we are getting there.”
MetLife Foundation has also awarded institutional grants to support scientists whose work shows promise for the future of Alzheimer’s disease research. Grants were made to the following institutions:

2014
Harvard Medical School Center for Neurological Diseases
Jie Shen, PhD

2012
Washington University School of Medicine St. Louis, MO
Randall J. Bateman, MD
Associate Professor of Neurology

2005
Ludwig-Maximilians-Universitat
Christian Haass, PhD
Professor of Biochemistry
Adolf-Butenandt-Institute, Muenchen, Germany

University of California, Irvine
Frank LaFerla, PhD
Professor, Department of Neurobiology and Behavior

2002
Washington University School of Medicine St. Louis, MO
David M. Holtzman, MD
Charlotte and Paul Hagemann Professor of Neurology

University of California, San Francisco
Lennart Mucke, MD
Director, Gladstone Institute of Neurological Disease
Professor of Neurology and Neuroscience

2000
Columbia University College of Physicians and Surgeons
Gary Struhl, PhD
Professor, Department of Genetics and Development
Investigator, Howard Hughes Medical Institute

Harvard Medical School
Li-Huei Tsai, PhD
Associate Professor, Department of Pathology
Assistant Investigator, Howard Hughes Medical Institute

1998
Columbia University College of Physicians and Surgeons
Iva Greenwald, PhD
Professor, Department of Biochemistry and Molecular Biophysics
Investigator, Howard Hughes Medical Institute

University of Minnesota
Karen Hsiao Ashe, MD, PhD
Professor Department of Neurology

1994
Harvard Medical School Center for Neurological Diseases
Jie Shen, PhD

1992
University of California, San Diego
Fred H. Gage, PhD
Professor, Laboratory of Genetics
The Salk Institute

University of Kentucky Medical School
Mark Mattson, PhD
Chief, Laboratory of Neurosciences
National Institute of Aging
Professor, Department of Neuroscience
Johns Hopkins University of Medicine

1991
State University of New York at Stony Brook
Dmitry Goldgaber, PhD
Professor, Department of Psychiatry and Behavioral Science

University of Pennsylania School of Medicine
Virginia M.-Y. Lee, PhD and John Q. Trojanowski, MD, PhD
Professors of Pathology and Laboratory Medicine
Co-Directors, Center for Neurodegenerative Disease Research

1989
Brigham Medical Center
Kenneth S. Kosik, MD
Professor of Neurology Harvard Medical School

McLean Hospital
Charles Marotta, MD, PhD
Chief, Molecular Neurobiology Laboratory
Professor of Neuroscience, Psychiatry and Human Behavior
Brown University

University of California, Irvine
Rachael Neve, PhD
Assistant Professor of Psychobiology
Associate Professor of Genetics
Harvard Medical School

1988
Columbia University College of Physicians and Surgeons
Iva Greenwald, PhD
Professor, Department of Biochemistry and Molecular Biophysics
Investigator, Howard Hughes Medical Institute