Gaining Momentum in Our Quest for Cures for Alzheimer’s, ALS, Huntington’s and Parkinson’s Disease

Developing a new drug can cost close to a billion dollars and take 15 years. And still, many drugs that make it all the way to testing in humans fail. We must do better. Challenging the status quo is the mission of the Mass General Institute for Neurodegenerative Disease. Dissatisfied with an inch-by-inch approach to curing disease, MIND leaders are determined to make a difference for this generation with better treatment and ultimately cures. MIND scientists are dedicated to innovative basic science and faster testing of treatment ideas early in the scientific process. Our efforts are succeeding, thanks to our committed patients, donors and friends.

In this year’s review, there are several stories about new therapeutic approaches—drugs, proteins, and genetic therapies. The foundation of all these ideas was creative, risky, and unglamorous basic science conducted at MIND’s laboratory benches by hundreds of young researchers guided by the world’s experts. We don’t yet know which ideas will work and which will fail. But because MIND has all the components necessary to test new ideas early, we can do it faster, before the price soars astronomically. And we will continually be at the laboratory bench, looking for another angle, and then another, again and again, until we cure these diseases.

The enormous cost for new drugs balances precariously on the quality and ingenuity of the basic research and drug discovery conducted at places like MIND. Donations large and small, often from patients who live heroically with these diseases, fund our most exciting work. It is this generosity and faith in MIND’s approach that inspires us to work harder and smarter, and to win the race to a cure. Thank you.

“Scientists feel motivated and fulfilled when their work helps patients. Donors, foundations, and funding agencies also know that a place like Mass. General is more likely to take breakthroughs and apply them immediately to save lives,” states Dr. Anne Young, chief of Neurology and director of MIND. Central to this mission is the Neurology Clinical Trials Unit, which rapidly brings new advances from the laboratory into testing in people with neurodegenerative disorders.

Massachusetts General Hospital has the largest hospital-based research program in the world, and was recently named the best place to work in academia, according to a survey by The Scientist magazine. The reason? Our patients.

“We are constantly amazed at the generosity and enthusiasm of patients who participate in studies to test new treatments,” stated Dr. Cudkowicz. “Patients and their families motivate and inspire us and directly help us evaluate new treatments by participating in our clinical studies.”

Right now, thousands of MGH patients from the neurology clinics are involved in clinical trials at the MGH to test new treatments in amyotrophic lateral sclerosis (ALS), Alzheimer’s, Mild Cognitive Impairment, Dementia with Lewy Bodies, Cerebral Amyloid Angiopathy, Parkinson’s, Huntington’s, and other neurodegenerative diseases.

MIND physicians also have been leaders in leading nonprofit clinical study groups in each disease area. Dr. Cudkowicz and Dr. Robert Brown started the Northeast ALS Consortium; other physicians are leaders in the Parkinson’s Study Group, the Huntington’s Study Group, and the Alzheimer’s Disease Research Centers. These nonprofit groups are committed to coordinating clinical trials with open and full scientific reporting of study results, and have many member centers that can quickly launch trials with hundreds of patients around the country.

Dr. Merit Cudkowicz leads the Neurology Clinical Trials Unit, which rapidly brings new advances from the laboratory into testing in people with neurodegenerative disorders.

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MIND’s Parkinson’s Disease Therapy Initiative took a leap forward when a collaboration between MIND’s drug discovery lab and several Parkinson’s disease scientists—Drs. Alex Kazantsev, Tiago Outeiro, Pamela McLean and Bradley Hyman (pictured clockwise at right) and Anne Young—led to the discovery of a potential new set of drug compounds for the treatment of Parkinson’s disease. This group’s work, which was published in the prestigious journal Science, showed that their drug called AGK2 blocks the action of an enzyme called SIRT2 and protects the neurons damaged in Parkinson’s disease in both cell and animal models. Inhibiting the enzyme saves cells from the toxic effects of alpha-synuclein, a protein that accumulates in the brains of Parkinson’s patients. The drug also could help treat other neurodegenerative diseases in which abnormal proteins accumulate in the brain, such as Dementia with Lewy Bodies, Huntington’s and Alzheimer’s.

“We have discovered a compelling new therapeutic approach for Parkinson’s disease, which we hope can treat and perhaps even cure this disorder,” says Alex Kazantsev, PhD, director of MIND’s Drug Discovery Laboratory. “Our discovery also will allow drug companies to seek their own SIRT2 inhibitors as potential PD drugs, which multiplies our efforts.”

This discovery demonstrates the power of the MIND model of collaboration. Initially, a research team led by Kazantsev was seeking drugs that would reduce protein accumulations in brain cells affected by Huntington’s disease. Out of 37,000 compounds they found one—B2—which acted like a trash compactor to clean up the cell by forming larger, but less toxic, inclusions. Collaborations with MIND’s PD scientists to test the compound in Parkinson’s disease cells proved successful—B2 kept PD brain cells alive.

Continued on page 2
Most cases of amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig’s disease) are sporadic, meaning that they don’t appear to be inherited. But we also know that, in addition to aging, there is a combination of genes and environmental factors at play that predispose certain individuals to the disease. Unlocking the mystery of ALS causation is the ultimate milestone on the road to finding a cure. “Since we can’t easily assess what someone’s lifetime environmental exposures may have been, and we can’t yet control aging, we must find the genetic influences that may make one person more susceptible to developing ALS, while a brother, sister or neighbor with common experiences remains unaffected,” stated Dr. Robert Brown, director of ALS research in the Day Laboratory at MIND.

The first genetic studies only were able to identify disease mutations that people could inherit with certainty—for example, cystic fibrosis, Huntington’s disease and rare familial forms of ALS. Now, a technological revolution in genetics allows scientists to search deep within the human genome to seek out the small mistakes or differences in DNA—that together with environment, aging and bad luck—could trigger the brain cell death found in ALS. An international consortium of committed scientists collected blood samples from ALS patients around the world. John Landers, PhD worked with Dr. Brown to compare these 2,000 samples with those from 2,000 people who did not have ALS. In the past, this work would have taken a scientist’s lifetime. Now, genome-wide association analysis can be done in a year with the use of gene chips, sophisticated robotic equipment and super computers. While still lengthy and exhaustive work, the amount of information collected is astounding.

Dr. Brown and Dr. Landers have completed the analysis and have found that there are indeed some candidate genes that appear to modify ALS in patients. They expect to publish the detailed results in early 2008. “We hope to catalyze a worldwide interest in studying these defects to see how they define and affect the disease pathway. Our expectation is that knowing the function of these defective genes will enable the discovery of drugs that could interrupt the cell death, or perhaps restore some functioning in ALS,” explains Dr. Brown.

Epidemiological Detective Work Uncovers New Drug Target for PD

Through a major collaborative effort between investigators at MIND and the Harvard School of Public Health, (HSPH) a powerful antioxidant known as urate has been identified as a possible biomarker for Parkinson’s and a new target for drug development. The discovery by Dr. Michael Schwarzschild and his colleagues is so ripe for translation into novel therapeutic strategies, that clinical trials to test a urate booster as a drug for Parkinson’s Disease (PD) could start as early as 2008.

Invaluable clues to Parkinson’s have been found in long term studies of large populations, providing a treasure trove of research ideas. Dr. Schwarzschild’s collaborators at the Harvard School of Public Health, led by Dr. Alberto Ascherio, work with MIND investigators to identify participants in these studies who develop PD as they reach their 50’s, 60’s and 70’s. They then look back in great detail to carefully compare these patients to those who did not develop PD, examining what they ate and drank, where they lived, what vitamins they took, and what was measured in their blood, all with the goal of finding new clues to how PD is triggered or prevented.

Most recently, Dr. Ascherio’s group at HSPH found a link between blood levels of a natural metabolite, urate, and a reduced risk of developing PD later in life. The preliminary analysis exalted Dr. Schwarzschild, who immediately wondered, “If higher urate levels among the healthy foretell a lower risk of getting PD, might higher levels among those already diagnosed predict a milder rate of its progression? If so, could urate actually protect brains of PD patients somehow?”

The next day he set out in pursuit of the answer. Dr. Schwarzschild knew that starting from scratch would be too costly and time consuming, so he looked for large clinical studies in which PD patients had been tracked for years, where urate levels had been incidentally measured or their body fluids had been stored.

Fortunately there were large collections of biological samples as well as clinical data from PD patients that have been saved for just such a purpose at the Parkinson Study Group, a consortium of PD clinical trial specialists from around the US and Canada. By examining existing blood and brain fluid samples from two previous clinical trials with more than 1,600 PD patients, Dr. Schwarzschild and his colleagues discovered that higher blood or brain levels of urate predict a substantially slower rate of progression of PD as measured by both clinical exams and brain scans.

The results were so compelling that urate is now the first known molecular predictor of disease progression in typical Parkinson’s disease, a major advance in the development of biomarkers and possibly protective therapies for PD. A clinical study to see whether manipulating urate levels with new or existing drugs could slow disease progression is currently being planned to launch in 2008, with funding from the Michael J. Fox Foundation.

“We’re in a great position to capitalize on this discovery at MIND, with our highly collaborative laboratory environment, epidemiology resources and clinical perspectives,” said Schwarzschild. “Now we will marshal the same resources to explore exactly how urate works as a protective influence on brain cells, in order to mine for additional treatment strategies.”
How Insults to the Brain Increase Risk for Alzheimer’s Disease

Strokes, head injuries, and general anesthesia are never pleasant experiences, but they also have long-term effects—all may contribute to an increased lifetime risk of Alzheimer’s disease (AD).

While many studies have demonstrated these links, researchers have never known exactly how risk is conferred. Investigators in the Genetics and Aging Research Unit at MIND, directed by Dr. Rudy Tanzi, are beginning to fit the pieces of the puzzle together, and the central player appears to be beta-secretase (BACE), an enzyme which can wreak havoc on the brain by releasing small fragments of the amyloid precursor protein, the main ingredient for Alzheimer’s plaques.

**STROKE**

Dr. Giuseppina Tesco and Dr. Rudy Tanzi have been examining the chemical events that precede an increase in BACE levels. In a healthy brain, a chaperone molecule called GGA3 helps to reduce excessive amounts of BACE by guiding it to the place in the cell where it is broken down. But following trauma, the brain tries to get rid of damaged brain cells by initiating programmed cell death. This includes the activation of caspases, enzymes that act as scissors to chop up proteins within the cell marked for death.

Dr. Tesco and her team found, in cells as well as rat brains, that these caspases also chop up the important GGA3 molecule, which interferes with its ability to break down BACE. BACE accumulates, activating a devastating downward spiral of amyloid build-up in the brain, plaque formation, and more cell death. By examining human post-mortem brain tissue, they were able to confirm that reductions in GGA3 corresponded with elevation of BACE, particularly in the areas most affected by Alzheimer’s plaques.

“The treatment that aims to preserve GGA3 following a stroke or head trauma could be a way to reduce the risk of AD later in life,” stated Dr. Tesco. This work was funded in large part by the Cure Alzheimer’s Fund.

**SEIZURES**

Dr. Dora Kovacs and Dr. Doo Yeon Kim have shown that in addition to interacting with APP, BACE has an important role in the electric wiring of the brain around the brain cell membranes, and may explain a higher risk of seizures in AD patients. Dr. Kovacs’ team showed that BACE can cleave nerve cell surface molecules called sodium channels, which control how nerve cells fire. They showed that excessive amounts of BACE can disrupt the normal electrical activity of these sodium channels, making nerve cells more vulnerable to aberrant firing and perhaps seizures.

Therefore, therapies aimed at BACE may not only treat AD, but may also be useful for mitigating seizures in AD patients.

**ANESTHESIA**

Dr. Zhongzeng Xie and Dr. Rudy Tanzi have shown that the common inhalation anesthetic isoflurane can also result in an increase in BACE levels, which may explain why elderly patients sometimes deteriorate cognitively after general anesthesia. As in the case of stroke and head trauma, the increased amounts of BACE driven by isoflurane was linked to programmed brain cell death, and then more amyloid is produced from the APP protein. Changes were most pronounced in cells where there was already significant accumulation of both APP and amyloid.

“While it may be a tipping point in the brain, where the addition of a marginal amount of amyloid to an already overloaded system may initiate a cascade of destruction, Right now we have only shown these effects in cells, and further study is needed to determine whether it has implications for humans and clinical practice.”

Taken together, these studies provide valuable new clues for how BACE inhibitor therapies, some of which are already in development, might be used for the effective prevention and treatment of AD.

Can Indian Curry Help Protect Against AD?

MIND researchers are on the quest for substances that can delay or treat AD and curcumin, a natural chemical that is found in the yellow curry spice turmeric, may hold one key.

Curcumin has been shown to reduce brain cell death in test tubes, but it was unclear what effect it would have in vivo—in live animals and ultimately humans.

Before drugs can be tried on humans they must undergo testing in other animal models—and mice are the usual surrogates. However, Alzheimer’s disease presents unique challenges in preclinical research because it’s difficult to test the cognition and memory of mice. In the past, physical changes in the brain had to be seen post-mortem.

Now, armed with microscopic equipment that can take astonishing photos of changes in the living mouse brain over time, MIND researchers, led by Brian Bacskai, PhD and Brad Hyman, MD, PhD are uniquely positioned to evaluate the effects of this and other potential therapeutics on mice that have a form of Alzheimer’s. Their group leads the world in the use of microscopic 2-photon imaging to document physical changes in individual brain cells and watch, in real time, therapies that prevent and even reverse the brain damage seen in Alzheimer’s.

Dr. Bacskai’s latest work is on a small molecule called curcumin which is the pigment that gives curry its distinctive color and also has anti-inflammatory and anti-oxidative properties. It is a natural, non-toxic product from plants, and can cross the blood brain barrier to bind to amyloid deposits and AD plaques. It is also fluorescent, so is easily measured by photo techniques.

His work shows that curcumin can prevent new AD plaques and actually clears existing plaques. It also can improve the brain’s signaling apparatus by straightening out neurites, the spider-like protrusions that help a brain cell send messages.

“Curcumin is being tested in patients with mild to moderate Alzheimer’s disease in a small clinical study in California, but results have not yet been published. It could be that the next steps would be to generate versions of curcumin that enter the brain more efficiently. In the interim, curry will be on the menu at MIND.”

For more information about MIND research, visit www.mind.org.

**ACKNOWLEDGMENTS**

This work was funded in large part by the Cure Alzheimer’s Fund.
Creative Approaches for Huntington’s Disease Therapies

Dr. Hersch now plans to confirm these positive results in a different mouse model with a longer life span, that may be a better predictor of disease progression in humans. He also will modify the C2-8 compound to see whether different iterations would be more potent. Most importantly, he will continue to examine how C2-8 slows down the disease by identifying interacting molecules in brain cells, which could open the door for further drug discovery.

Silencing the HD Gene

Marian DiFiglia, PhD has collaborated with University of Massachusetts Medical School to demonstrate how therapies might be able to completely shut down the mutant Huntington’s disease gene, protecting brain cells from the lethal form of protein encoded by the gene. This approach is called RNA interference, a cutting edge technology which captured the 2006 Nobel Prize and works by silencing the mechanism for the production of protein. Proteins are encoded on DNA, and messenger RNA’s provide the blueprint for the assembly line process—so shutting down RNA is like throwing a wrench in the assembly line to prevent the production and accumulation of toxic proteins.

In Dr. DiFiglia’s research, the mutant HD gene was inserted into mouse brains, which causes the mouse to develop a very severe case of HD in a short period of time. She then injected a newly designed form of RNA, called small interfering RNA (siRNA) to see if it could block the action of the mutant HD gene.

The mice that were treated with siRNA directed to the HD gene demonstrated significantly improved motor symptoms of the disease compared to mice tested with control siRNA. Some functioning was actually restored by blocking HD protein synthesis.

“We show that RNAi is a feasible approach for an HD therapeutic, which is an exciting possibility. Our particular method of using siRNA also has the advantage of being amenable to changes in dosing. This RNAi is cleared from the brain eventually, which we hope would reduce the risks of side effects,” stated Dr. DiFiglia.

The next challenge in testing siRNA therapeutics in human brain disease will be developing safe delivery methods and capability for RNA’s to distinguish between mutant and normal genes.

Epigenetics – At the Vanguard of Brain Disease Research

Dr. Jang-Ho Cha is combining creative thinking, novel technology, and collaboration with MIND colleagues to better grasp the intricate role that abnormal proteins play in the genetic changes observed in neurodegenerative disease. This rapidly emerging field is called “Epigenetics”—the interplay of molecules in cells that control the actual functioning of the genetic code.

Epigenetics builds upon the findings of the Human Genome Project, which stunned the world with evidence that humans have roughly 25,000 genes, much fewer than expected. “A profound shift is happening—we now see that the secrets of human disease lay not only in abnormal disease genes, but also in the functioning of normal genes that are turned on or off at the wrong time,” said Dr. Cha.

Better understanding of how and why genes are transcribed or shut down has led to breakthroughs in cancer research, where the wrong signals tell tumor cells to replicate and grow. Dr. Cha and others at MIND believe it also has implications for neurodegenerative disease where the opposite is true—bothered signals tell brain cells to wither and die prematurely. MIND provides the unique mix of brain power and expertise to discover how and why this happens.

Sweeping technological changes in life sciences are harnessed at MIND with the use of new “ChIP-on-chip” techniques. In this approach, specially prepared pieces of DNA which are bound to a specific protein are overlaid onto chips the size of a postage stamp that hold thousands of genes in a grid. Locations where the protein attaches light up, providing a bird’s eye view of the entire genome and its relationship to the suspect protein.

Dr. Cha’s group was the first to use this technique in Huntington’s disease, and now is collaborating with Drs. Pamela McLean, Anne Young and Ippolita Cantuti-Castelvetri in Parkinson’s disease, Dr. Robert Brown in ALS, and Dr. Suzanne Guenette in Alzheimer’s disease. Sophisticated analysis is provided by MIND’s Center for Interdisciplinary Informatics, led by Tim Clark. These scientists hope to uncover whether and where notorious proteins such as alpha-synuclein in Parkinson’s, SOD1 in ALS, and F655 in Alzheimer’s disease may interact directly with DNA. Ultimately, this team effort is expected to lead to smarter drugs that inhibit the action of specific gene-altering molecules, a radically new approach to treating and curing disease.

Jang-Ho Cha, MD, PhD

Epigenetics technology: Genes bound to proteins expressed in cells (proteins colored pink in the black circle) are applied to gene chips (rectangle). Each gene where the protein attaches lights up as a dot on a grid and the final result is a map of the entire genome with all the protein binding sites, (shown in the background).