MASSACHUSETTS General Hospital attracts people from around the world searching for outstanding patient care. Behind the scenes is the hospital’s vast research enterprise, driven by scientific talent that is fiercely determined to understand, treat and cure disease in new ways.

MIND, the MassGeneral Institute for Neurodegenerative Disease, is a flagship in this effort with more than 200 researchers making groundbreaking discoveries in Alzheimer’s, Parkinson’s, ALS, Huntington’s and other brain diseases. Our 25 laboratories in the Charlestown Navy Yard are humming with activity as senior investigators lead fellows, students and technicians on a journey to conquer these diseases.

I am particularly inspired by the enthusiasm of newly minted neuroscientists and neurologists who move to Boston to work at MIND, bringing boundless enthusiasm and stamina for long nights at the laboratory bench. Their inspiration, in turn, is the grace and courage shown daily by our patients.

It’s not just inspiration that makes MIND work, however. Every patient is an essential partner in our effort. Together, you fuel our engine of discovery and sustain our efforts. Thank you.

Like a canary in a coal mine, a patient’s sense of smell is often the first indicator of Alzheimer’s or Parkinson’s disease. Because smell is controlled by a small set of neurons that are vulnerable to the same disease processes that wreak havoc on cells deep in the brain, it declines before obvious memory or motor symptoms occur.

Fortunately for MIND, our newest investigator, Mark Albers, MD, PhD has expertise in olfaction (sense of smell) acquired in the laboratory of Nobel laureate Richard Axel, MD at Columbia University. Dr. Albers’ laboratory exploits the simplicity of olfactory neurons to decode neurodegenerative processes and their response to treatment.

Dr. Albers’ preliminary work at MIND was so impressive that the National Institutes of Health granted his group the prestigious, five-year Innovator Award for exceptionally creative and high impact projects.

Olfactory neurons are an efficient proxy for brain cell death. “Since the neurons that constitute the smell system are arrayed in an easily decipherable map, and they are located close to the surface of the skull, we can visualize them easily, and see the effect of new treatments,” says Dr. Albers.

Testing a mouse’s finely tuned sense of smell provides a behavioral indicator of olfactory neuron health. Dr. Albers’ laboratory created a mouse house with two distinct smell chambers. Naturally curious, a normal mouse will investigate the space, but once it enters a chamber that smells of fox urine, it freezes and then scurries out into a far corner. A mouse expressing an Alzheimer’s gene only in the olfaction system will explore the chamber but demonstrates a much-delayed reaction to the fox smell, if at all.

Microscopic imaging is another way to reveal the damage to the olfactory neurons. Coupled with post-mortem biochemical analyses, Albers’ work provides a rich description of disease related changes in the neurons and how they affect behavior.

These experiments also provide an efficient way to test potential new drugs. Albers’ group is collaborating with MIND investigators Dr. Michael Schwarzschild and Dr. Pamela McLean to use this approach with genes associated with Parkinson’s disease.

“We plan to administer potential therapies to the mice to see if they will save neurons, and test the mouse’s sense of smell after administering the drug,” says Dr. Albers. (continued on page 4)
Testing new drugs for ALS

In the quest for better treatment, rigorous analysis of a potential drug’s effectiveness and safety is essential. “Fifteen years ago, there was no treatment for ALS and not much to try. Now, research discoveries are so numerous that we have to prioritize the most promising ideas,” says Merit Cudkowicz, MD, director of the Mass General Neurology Clinical Trials Unit.

“We feel a great urgency to find new therapies for ALS and that means quickly identifying drugs that should move forward and those that are ineffective,” she adds. In the last year, three drugs illustrate the unit’s approach.

Ceftriaxone moves forward

In an effort to efficiently identify existing drugs that could be repurposed for ALS, researchers tested all drugs approved by the U.S. Food and Drug Administration (FDA) in a cell-based experiment to see which might protect motor neurons. Ceftriaxone was a “hit” in this screen and subsequent testing in the laboratory and ALS mice showed that it may help clear the neurotransmitter glutamate near nerve cells, protecting them from toxic over-excitation.

Although ceftriaxone is approved by the FDA for treating acute bacterial infections, Phase I and II trials were necessary to show that the drug was safe for ALS patients and that it could enter the cerebrospinal fluid where the motor neurons function. These trials were successful.

The Phase III trial, which is enrolling up to 600 people at multiple sites in the U.S. and Canada, will determine the efficacy of ceftriaxone for ALS.

Antisense drug ISIS-SOD1Rx begins Phase I clinical study in familial ALS patients

The explosion in genomic information has led to the discovery of many new disease-causing proteins. A new class of drugs called antisense molecules bind to messenger RNAs (mRNAs) and inhibit the production of disease-causing proteins.

Isis Pharmaceuticals is sponsoring a Phase I study that will evaluate the safety, tolerability, and pharmacokinetics of a new investigational drug, Antisense oligo ISIS 333611. It will be administered intrathecally (using a pump and a catheter to deliver medication into the spinal fluid) to patients with rapidly progressive forms of familial amyotrophic lateral sclerosis (ALS) due to mutations in the SOD1 gene.

Lithium shows no benefit

Investigators and funding organizations joined forces to rapidly replicate an intriguing study from Italy that showed a positive effect of the drug lithium in a small group of ALS patients. Because the results were so striking, many patients were eager to begin treatment with the drug, but a larger study was needed to confirm the results.

Swati Aggarwal, MD and Dr. Cudkowicz, in partnership with the Northeast ALS and the Canadian ALS consortia, quickly launched a randomized trial that enrolled 84 people over four months. Neither the patients nor the physicians knew who was receiving lithium. Unfortunately, the blind study did not show a beneficial effect of lithium on the progression of ALS and was consequently halted.

“Although we were disappointed, it is essential that patients have good information about what works and what doesn’t. We will continue to forge ahead on potential drugs using the best approaches we have. We are so grateful for those patients who are willing to volunteer for clinical studies who make this work possible,” says Dr. Cudkowicz.
Drug discovery gaining ground

Alex Kazantsev, PhD prefers a leather jacket to a lab coat and resembles a made-for-TV spy as he spends evenings intensely studying screens filled with computer-generated chemical structures. His obsession? Finding the perfect molecule that will rescue brain cells from the malfunction and death that is the hallmark of all the neurodegenerative diseases. As MIND’s drug discovery expert, Dr. Kazantsev is steadily gaining ground in this battle.

“We created MIND to take advantage of the commonalities in these diseases and find treatment faster,” says Anne Young, MD, PhD, founder of MIND. “We raised funds from our patients and recruited Alex Kazantsev to make this a reality, and our investment is paying off with tangible results.”

Rather than focusing on a single disease, Dr. Kazantsev works collaboratively with MIND’s scientists, taking their models and adapting them for large-scale automated drug screens as well as smaller secondary studies. Perseverance and intuition have led to early successes in identifying molecules that continue to pass the numerous hurdles of drug development.

From Russia to MIND

It has been a long path from Dr. Kazantsev’s childhood home in Moscow, Russia, to MIND. After earning a doctorate from the University of North Carolina, he was a postdoctoral fellow at the Massachusetts Institute of Technology, where he optimized a Huntington’s disease assay for drug discovery. To his dismay, numerous meetings with drug companies yielded no progress in bringing treatment ideas forward to patients.

“We needed more proof and validated targets to entice companies to invest in brain diseases,” explains Kazantsev.

His work at MIND has focused on providing that proof. Dr. Kazantsev’s group initially identified a drug compound that protected Huntington’s disease cells by cloistering the toxic proteins into manageable packages. The compound also worked in Parkinson’s and Lewy Body disease cells.

However, the drug’s actual target was unknown. Dr. Kazantsev’s epiphany was when he discovered the exact enzyme — called Sirt2 — that the drug was inhibiting, which led to the identification of even better compounds.

A drug development program is now moving forward in several diseases. MIND’s research group led by Dr. Pamela McLean, PhD is testing the compound in rodent models of Parkinson’s and Lewy Body disease, while Tara Spires-Jones, PhD is administering it to mouse models of dementia. Dr. Kazantsev’s next goal is ALS.

Obtaining resources for drug discovery, which falls into the black hole between basic science and clinical research for patients, is always a challenge. Fortunately, private donations to MIND from individuals and the Michael J. Fox Foundation and other groups, have kept MIND’s drug discovery effort operational.

Dr. Kazantsev reveals a philosophical belief in the promise of his efforts: “It used to be that a rabbi or priest or physician really made a difference in a person’s life. Today, a molecular biologist can join forces with these healers. I feel it’s an obligation to use my skills and my training in this way for patients.”
Healthy synapses... healthy brains

It’s no surprise that Alzheimer’s disease (AD) compromises brain circuitry, but exactly how the disease process interferes with memory formation and recall is still a crucial question. The answer could lead to new therapies, so MIND investigator Tara Spires-Jones, DPhil, working with medical and doctoral student Robert Koffie, is discovering important details about how AD could obstruct the complex signaling between cells.

Brain cells called neurons must “talk” to each other to function properly. A neuron has a long axon that reaches out and sends chemical signals over a tiny space called a synapse, which connects to a receiving arm, called a dendrite, on another nerve cell. Changes in size, strength, and numbers of synapses allow the healthy human brain to learn, form memories, and respond to the environment. Conversely, brains ravaged by AD are characterized by a sharp reduction in synapses.

Dr. Spires-Jones and Koffie are using a cutting edge technique called array tomography to study synapse loss in AD mice and how it relates to amyloid beta, the toxic protein that can clump together to form Alzheimer’s plaques in the brain.

“Amyloid beta is sticky, and many thousands of copies of the amyloid beta peptide gather together to form plaques, but even a few of these peptides stuck together in small groups can be harmful. In fact, current thinking is that these small pieces — called oligomers — may actually be more toxic to the cell than big plaques,” states says Spires-Jones.

Spires-Jones and Koffie showed that amyloid beta oligomers tend to cling to the receiving end of synapses—the postsynaptic density — and that this association coincides with synapse shrinkage and death in AD mice. “This was a revelation because it links amyloid pathology, one of the hallmarks of AD, to synapse loss, which can directly cause dementia,” says Spires-Jones.

“We also see this as an opportunity for treatment because synapses are very resilient and able to recover—unlike the neurons themselves which are very hard to replace,” adds Spires-Jones. In support of this idea, Dr. Spires-Jones found that removing oligomers with an antibody increases the number of synapses in AD mice, providing hope for functional recovery.

Smell studies travel from the lab to the clinic

Dr. Mark Albers (see cover) is rapidly bringing one aspect of his olfaction work to MGH outpatient clinics. He is assisting in the development of a computer-based “smell test” screening tool to identify which odors are best used with patients to detect smell deficits that are early indicators of neurodegeneration. Ultimately, a quick odor panel may help primary care physicians identify patients who should be referred for early testing and treatment for Alzheimer’s or Parkinson’s disease before the onset of memory or motor symptoms.
MIND’s Rudy Tanzi a “Rock Star of Science”

Rudy Tanzi, PhD gave up playing keyboard in a rock band to pursue a doctorate in neuroscience in the 1980’s, so he never imagined Alzheimer’s research could put him on a stage with Aerosmith’s Joe Perry. Adding another distinction to his scientific career, Dr. Tanzi, director of the Genetics and Aging Unit at MIND, joined musicians Joe Perry, Sheryl Crow, Will-I-am, Josh Groban, and Seal, in a designer photo shoot as a “Rock Star of Science” in GQ Magazine, and shared the stage with Joe Perry in a music video and concert.

“Rock Stars of Science,” a new public service campaign sponsored by GEOFFREY BEENE GIVES BACK® and GQ Magazine, spotlights the need for greater funding for medical research and works to make science a more attractive career choice for young people. During the campaign launch on Capitol Hill, Dr. Tanzi’s musical chops came in handy when he ditched his lab coat for a microphone and harmonica, livening up a jam session with Perry and Francis Collins, MD, PhD, director of the National Institutes of Health.

“Important medical breakthroughs are impossible without broad public support, and support needs mainstream recognition,” says Dr. Tanzi. “If medical and scientific research could get the same attention as a great band like Aerosmith, just think how much faster we’d be able to raise the funds needed to cure diseases like Alzheimer’s.”

In addition to his designation as a Rock Star of Science, Dr. Tanzi and his team are continuing to investigate the genetics involved with late-onset forms of Alzheimer’s. His 2008 discovery of four genes that may significantly increase risk was named one of the “Top Ten Medical Breakthroughs” of the year by Time. The four suspect genes are now being characterized to determine their pathological roles in Alzheimer’s disease with the hope of developing novel therapies for Alzheimer’s disease.

These new discoveries dovetail neatly with other research efforts in the Genetics and Aging Unit. A project led by Rob Moir, PhD is uncovering the normal function of the amyloid beta protein within the innate immune system, while other investigators are examining the relationship between AD and head injuries, stroke and general anesthesia.

Hopefully, Dr. Tanzi’s experience will be a great lesson to young people that being a rock star and a scientist are not mutually exclusive goals!
Largest-ever drug trial launched in Huntington’s disease

Development of a new drug is an arduous and complicated process. It is even more challenging if the drug is a nutritional substance, such as creatine, that cannot be patented and therefore lacks significant backing from a pharmaceutical company. Add an orphan disease like Huntington’s to the endeavor and the hurdles are enormous.

However, dedication and a compelling scientific foundation have enabled the launch of the largest therapeutic trial to date for Huntington’s disease (HD), which is being led by MIND investigators Steven Hersch, MD, PhD, and Diana Rosas, MD. This study, a definitive test of whether high-dose creatine can slow the progression of HD, is in collaboration with the Huntington’s Study Group and funded by the National Institutes of Health, the National Center for Complementary and Alternative Medicine (NCCAM) and the U.S. Food and Drug Administration (FDA) Orphan Products division.

Creatine is a natural substance that can help supply energy to cells and also reduces oxidative stress to brain cells. In HD, brain cells run out of energy, hastening their degeneration. Earlier studies using creatine with HD mouse models as well as smaller pilot clinical trials led by Drs. Hersch and Rosas demonstrated impressive results.

“Large amounts of creatine have to be ingested in order for therapeutic levels to reach the brain, so safety was a big concern,” says Dr. Hersch. “However, our Phase II trial with only 10 patients showed that high levels were safe and reached the brain. We were also amazed to see that a blood biomarker that detects brain degeneration was normalized, and brain imaging showed a slowing of brain shrinkage.”

Now, 650 patients from 44 sites around the world will test whether creatine monohydrate can slow the progression of HD in comparison to a placebo. The trial will take five years and millions of dollars to determine whether the biological effects that were observed in the small trial will translate to significantly slowing down disease progression and maintaining the quality of life for patients with HD.

New target for drug discovery

Protein misfolding and accumulation in brain cells is the hallmark of all neurodegenerative disease. Researchers from MIND have been looking at many different avenues to prevent or reverse these toxic processes, and now may be one step closer. Ideally, researchers would like to stimulate brain cells to use natural mechanisms to identify abnormally folded proteins and degrade and recycle them into less toxic forms.

Dimitri Krainc MD, PhD has identified a new strategy for removing the abnormal protein that causes Huntington’s disease (HD) from brain cells. In a 2009 issue of the prestigious Journal Cell, MGH researchers describe how altering the mutated form of the huntingtin protein appears to accelerate its breakdown and removal through normal cellular processes.

“One of the major challenges has been how to activate degradation machinery that only removes the disease-causing proteins and leaves normal proteins untouched,” says Dr. Krainc, who led the study. “We identified a mechanism whereby modification of the disease-causing protein itself facilitates the cell’s method of digesting and recycling the mutant protein.”

The MIND team found that a standard protein modification process called acetylation appears to flag mutant huntingtin molecules for removal from brain cells without affecting the normal version of the protein. It also improved neuronal function and prevented neurodegeneration.

“Among several candidate HD drugs currently in development are some that increase acetylation,” says Krainc. “But we need to identify more specific versions of these drugs that target only the mutant protein and don’t affect other cellular pathways. In addition to huntingtin, we are examining whether acetylation of other proteins affects their degradation in Parkinson’s and Alzheimer’s disease.”
Back to the future in Parkinson's disease

Sometimes the rear-view mirror provides an excellent view. At least that was the case when MIND’s Michael Schwarzschild, MD, PhD began looking back to analyze stored data from Parkinson’s trials, in partnership with the Harvard School of Public Health. By examining data from a clinical trial performed in the 1980’s, Dr. Schwarzschild’s group has found additional evidence that elevated levels of the antioxidant urate may slow the progression of Parkinson’s disease (PD).

“Urate is a major antioxidant and it can protect brain cells in a test tube,” he says. “This molecular evidence from Parkinson’s disease patients strengthens the possibility that it could be protective and help slow down the disease. The convergence of these laboratory and epidemiology findings has prompted us to move quickly to clinical trial to begin testing this possibility.”

“But we don’t yet know if it is urate itself or some related factor that helps people with Parkinson’s — so we are also keen to take this clue back to the into lab at MIND to better understand and refine the therapeutic strategies we’re pursuing,” adds Dr. Schwarzschild.

The current study reviewed information from a trial that had tested the drug deprenyl, now an established treatment for PD. The researchers analyzed samples of both blood and cerebrospinal fluid from 800 participants in the DATATOP study, conducted by the Parkinson’s Study Group in the late 1980’s.

Confirming the results of their groundbreaking 2008 study, Dr. Schwarzschild and Alberto Ascherio, MD, DPH found that participants with the highest blood urate levels had a 36 percent lower chance of needing to begin treatment during the two-year study period than did those with the lowest urate levels.

With the support of the Michael J. Fox Foundation, Dr. Schwarzschild and Dr. Ascherio, along with Parkinson Study Group colleagues from across the country, are conducting a multicenter Phase II trial at 10 centers. Enrolling 90 recently diagnosed patients, the SURE-PD trial will investigate whether treatment with the urate precursor inosine can safely increase urate levels with a goal of slowing disease progression.

“Because elevated urate levels have known health risks, including gout and kidney stones, urate elevation should only be attempted in the context of a closely monitored clinical trial in which potential benefits and risks are carefully balanced,” says Dr. Schwarzschild.

These exciting discoveries have shown that ideas for treatment can come from many sources, and that sometimes looking back can show the best way forward.
Families that are affected by Alzheimer’s, ALS, Huntington’s, Parkinson’s and other neurodegenerative diseases can make an important contribution to help speed up research. This year, two family foundations have joined forces to ensure that every gift to MIND will have double the impact.

Among our supporters are the Carmen Foundation and the Philly & Charlie Dake Foundation, both of which generously have offered to match contributions to any of MIND’s research funds this year. These families are affected by neurodegenerative disease and want to inspire others to invest in MIND’s approach.

“The reason the Carmen Foundation is placing so much confidence in Dr. Anne Young and her valiant crew is that MIND is an ‘umbrella-like’ structure held by a common handle: a collaboration of researchers from all over the world, dedicated to accelerating the development of treatments for brain disorders such as Parkinson’s, Alzheimer’s, Lewy Body dementias, Huntington’s disease and ALS,” says Marjorie Carmen, who started the foundation with her late husband, Milton Carmen. “How can we not afford to support this monumental research when more and more people are falling victim to neurodegenerative disorders?”

The Philly and Charlie Dake Foundation supports a wide range of educational and health organizations and has a longstanding interest in Huntington’s disease research. The Dake family owns and operates Stewart’s Shops, a chain of more than 300 convenience stores located in upstate New York and Vermont.

“Philly, her late husband Charlie and the entire Dake Family are known for their generosity and commitment to give back to their community,” says Dr. Young. “Philly was enthused about the opportunity to join with the Carmen Foundation to encourage our donors to contribute in spite of the difficult economic downturn. We are so grateful for the Dake and the Carmen Foundations’ creative approach to philanthropy.”

Contributions to MIND are essential to encourage unconventional approaches to intractable research problems and respond to new discoveries as they arise. MIND’s drug discovery program is completely supported by funds from individuals and foundations. Continued support will help us move disease research forward quickly, confidently and successfully. Make a gift today and double your impact, knowing it will be matched by these generous families.

Why Support MIND?

This year, there’s an even better reason: Any gift you give will be matched by two generous family foundations.

Your donation will be put to use right away for the most pressing research at MIND. Planned gift arrangements also are important to the MIND program because they provide a future funding source. To learn more about either giving opportunity, please contact Shawn Fitzgibbons, assistant director of Major Gifts, at 617-643-0447 or sfitzgibbons@partners.org, or Kathleen Duffy, director of Planned Giving, at 617-726-6675 or kduffy1@partners.org.