

## Research advances 2003

### ***Drug Screening Laboratory Opens***

A centerpiece of the Institute's mission to find treatment for neurodegenerative disease is our new drug screening laboratory which gives investigators access to the advanced drug development techniques of biotech companies. The laboratory opened in the spring and completed its first large-scale screen in the fall of 2003. Using "high throughput" robotic technology capable of screening thousands of samples a day, MIND scientists are seeking drugs that can slow or halt the neurodegenerative disease process. Currently 12 different screening projects are in various stages of development.

### ***4-D Imaging may lead to test for Alzheimer's disease in humans***

As seen in the PBS documentary "The Forgetting," Dr. Brian Bacskai, working in Dr. Brad Hyman's laboratory, reported exciting news of a new technique to detect the presence of the Alzheimers' related plaques in the brain. By injecting a nontoxic dye into mice, and using a highly sensitive microscope to view cells in the mouse brain, researchers were able to observe the dye cross the blood brain barrier, attach to amyloid plaques, and then slowly clear. By imaging the mouse brains over time, the researchers were able to see if and where plaques are formed and how they might be reversed. The dye is now being tested in humans using PET scanning devices and could lead to a diagnostic scan for AD in a year. Moreover, this new technique enabling researchers to track changes over time at the cellular level holds promise for many more research endeavors, especially those related to testing new drugs.

### ***The caffeine connection in Parkinson's disease***

Dr. Michael Schwarzschild has helped establish adenosine blockers – caffeine-like molecules that block aberrant brain signals in Parkinson's disease – as one of the most promising and realistic new therapies for PD. His laboratory discovered that adenosine blockers can prevent in mice the same type of brain chemical deficiency that develops in PD patients. These research findings in animals converged with recent human epidemiology studies linking caffeine consumption with a lower risk of PD, and raise the possibility that adenosine blockers may not only relieve symptoms of PD but could actually slow progression of the disease. His group has accelerated research into the role of adenosine in PD by developing genetically altered mice that lack adenosine signals in brain. Using these powerful research tools, the Schwarzschild lab now seeks to understand how adenosine blockers prevent brain cell degeneration, and is also exploring their potential for treating the disabling motor complications that can develop in PD patients.

### ***Genes found for late-onset Alzheimer's disease***

The recent PBS documentary "The Forgetting" featured an historical perspective on Dr. Rudy Tanzi's highly fruitful research program on AD gene identification, highlighting how these genes have facilitated the development of new treatments for AD. Having already been involved in identifying three AD genes, Dr. Tanzi has been actively searching for gene defects on chromosomes 9 and 10 associated with the common late-onset form of AD. His laboratory has now identified these genes as the insulin degrading enzyme (IDE) on chromosome 10 and *ubiquilin* on chromosome 9. The IDE gene provides an explanation for the known connection between AD and diabetes, since IDE is able to degrade both insulin and the Abeta protein that makes up Alzheimer's plaques. Dr. Suzanne Guenette's lab also showed that mice lacking the IDE gene show features of both AD and diabetes. Dr. Tanzi's lab has also discovered a third AD gene in collaboration with Dan Geschwind at UCLA: *glutathione synthase kinase 3-beta* appears to increase risk for AD and frontal lobe dementia in several different families.

### ***ALS genes and new theories on neuromuscular diseases***

Dr. Robert Brown and his team were part of a group that found the location of two as-yet-unidentified ALS genes lying within a small region of chromosomes 16 and 20. These genes are likely to yield significant information about how the disease can be caused and to broaden the applications of diagnostic and predictive testing for ALS. Another significant finding in the laboratory, in studies headed by Dr. Niall Lennon, concern a protein called dysferlin, whose deficiency causes two rare types of muscular dystrophy. Dr. Lennon has discovered the function of dysferlin as a skeletal muscle membrane repair protein, implying that muscular dystrophies can arise from failures of muscle cell repair. This completely novel concept will lead to new pathways for research and treatment.

### ***Finding and testing new drug candidates for Huntington's disease***

In 2003, ideas from the basic research laboratories advanced into the field of clinical therapeutics for HD. In MIND's drug development laboratory, an extensive screen of 30,000 drug-like compounds yielded five candidates that slowed HD disease progression in the test tube and are now undergoing secondary analysis in the laboratories of Drs. Jang-Ho Cha and Steven Hersch. Two compounds from a previous screen have successfully passed secondary analysis and will begin being tested on HD mice in our animal laboratories. In addition, in collaboration with other clinical centers around the country, we have completed a dosing and tolerability trial of minocycline in HD patients, an anti-inflammatory drug that has shown promise in mouse testing.

### ***Testing a promising new drug for Alzheimer's based on research at MIND***

As described in a front page story in the *Wall Street Journal*, discoveries made ten years ago by Dr. Ashley Bush and Dr. Rudy Tanzi about the role of zinc and copper in the development of Alzheimer's plaques in the brain have led to the testing of new drug. The antibiotic Clioquinol was tested in a very small clinical trial in Australia with promising results. It was the first clinical trial of an AD drug to effectively lower Abeta – the protein that forms plaques – in the blood of patients and show a correlation with cognitive improvement in AD. The results were encouraging enough that a larger trial is now being planned in the US.

### ***New genetic information yields clues on PD***

Parkinson's disease has long been considered a "non-genetic" disease, but recent discoveries have revealed an important role for genes and family history. Genetics is particularly likely to play a strong role when the symptoms of Parkinson's begin before age 50. Investigators at MIND including Drs. David Standaert, Anne Young and Brad Hyman are using these new genetic discoveries to produce models of Parkinson's disease in animals and study the basic causes of the disease. They are applying advanced optical and molecular techniques to these models, and have gained important insights into what goes wrong in Parkinson's disease. The overall goal of this work is to find a treatment that prevents or slows the progression of the disease.

### ***Dr. Anne Young elected president of worldwide brain research organization***

The prestigious Society for Neuroscience, the world's largest organization of 34,000 scientists dedicated to the study of the brain and nervous system, recently elected MIND's Scientific Director and MGH Chief of Neurology, Anne Young, MD, PhD, its president. She also just finished her term as president of the American Neurological Association, the oldest neurological organization in the world. Dr. Young is the first person to be president of both renowned organizations and has used these positions to advocate for increased attention to disease related research that blends basic science with the development of therapeutics and other clinical applications for patients.