It isn’t among the most obvious symptoms of Parkinson’s disease, unless you’re one of the nearly one million people in the U.S. who have it. While tremors are the most visible sign, more than 90 percent of Parkinson’s patients also suffer gastrointestinal disorders, including constipation and difficulty swallowing. Matthew Benskey wants to know why and what can be done to prevent or alleviate those symptoms. “A lot of patients say those symptoms are more debilitating than the motor symptoms,” he said. Working in the laboratory of his colleague Fredric Manfredsson, Benskey determined that the same kind of molecular changes in the brain that are associated with tremors, stiffness and slow movement also are occurring in the intestinal track. Among Parkinson’s patients, a protein in the brain called alpha-synuclein clumps up, leading to the death of brain cells that produce dopamine, a neurochemical necessary for normal motor function. “The same clumping of alpha-synuclein is happening to neurons throughout the esophagus, stomach and colon,” Benskey said. “When the alpha-synuclein is clumped up, it can’t do its normal function. Now the question is why? How does it happen? The goal is to find out what is going on in those cells to cause that dysfunction and figure out how to maintain normal function.” That will involve developing a treatment to maintain precisely the right amount of normal alpha-synuclein either through drug therapy or genetic engineering. “It’s kind of like the Goldilocks thing,” Benskey said. “You don’t want too much alpha-synuclein or too little of it.” While new treatments likely are years away, he and other researchers are experimenting with modified viruses, called viral vectors, to carry genetic material that when administered to patients could counteract the processes that cause Parkinson’s symptoms. “We are able to reverse engineer viruses to have them deliver a specific gene. That’s our bread and butter. That’s the tool we use.” He’s passionate about unraveling the mysteries of Parkinson’s and developing new and better treatments, he said, adding that “if it helps people, that is something worth working toward.”
Alison Bernstein concedes she wasn’t all that fond of biology in high school. Fortunately for those afflicted with Parkinson’s disease, her interest has taken a 180 degree turn. After receiving her undergraduate degree in biology, Bernstein earned her Ph.D. in genetics and neuroscience.

“I just love science,” she said, particularly the specialized field of epigenetics, the study of how cells can alter gene expression without changing the genetic code itself. Epigenetics can be affected by such environmental factors as stress, diet, behavior and toxic exposures, which can change gene expression and, in some cases, trigger diseases.

Five to ten percent of Parkinson’s cases are familial, meaning they are inherited. The remaining 90-95 percent are sporadic, but still could have a genetic link, Bernstein said. Someone might have a genetic predisposition to Parkinson’s but never develop the disease unless exposed to an external factor.

“There is this piece of the risk that is not exclusively related to genetic factors,” Bernstein said. “A lot of researchers, including me, think it’s this convergence of the environment and your genes. Everything that you eat, whether you exercise or have a toxic exposure, can affect your genome.” Some studies suggest that people living in rural areas are slightly more susceptible to Parkinson’s, possibly because of exposure to pesticides, such as DDT, that were used in the 1960s and 1970s, she said. That class of chemicals, known as organochlorines, accumulates in the brain.

Part of Bernstein’s research is into how exposure to such pesticides alters the neurons in the brain that produce dopamine, a chemical that declines in Parkinson’s patients. She also studies brain tissue from deceased Parkinson’s patients, looking for DNA changes. She and Jack Lipton, chair of the Department of Translational Science & Molecular Medicine, also are collaborating on a study of how maternal exposure to the drug ecstasy affects the fetal brain.

Looking at Parkinson’s as more than just a genetic disease “helps us expand our net so we can look for new drug targets,” Bernstein said. Knowing that her work can help Parkinson’s patients “is what gets us out of bed every morning,” she said.

“Everything that you eat, whether you exercise or have a toxic exposure, can affect your genome.”
Tim Collier believes he and a former colleague have found a new use for an old drug that could be the first treatment to slow the deterioration of Parkinson’s disease. He hopes to begin clinical trials soon.

That approach fits with Collier’s bench-to-bedside philosophy, quickly and safely translating discoveries in his laboratory into treatments for patients. “At present there is no treatment that affects the progression of the disease,” said Collier, who holds the Edwin A. Brophy Endowed Chair in Central Nervous System Disorders. “What this could do is slow the progression of the disease so that it could be treated with other drugs,” in effect making it a chronic but treatable condition and allowing patients to outlive their disease.

The drug, nortryptiline, was approved by the Food and Drug Administration 40 years ago to treat depression. Collier and former colleague Katrina Paumier studied nortryptiline as a possible Parkinson’s drug. (Paumier, now on the faculty at Washington University in St. Louis, continues to collaborate with Collier.)

“It was becoming more and more clear that Parkinson’s disease was not just a movement disorder,” Collier said, “but that it had a lot of co-morbidities” or other symptoms, including depression. “It probably should be called ‘Parkinson’s diseases,’” he said, because its causes and progress varies considerably from one patient to another. That might be why nortryptiline appears to work against Parkinson’s, he said, since, as an early antidepressant, it hits a lot of targets in the brain. Newer antidepressants are more narrowly focused.

In the laboratory, Collier and Paumier showed that nortryptiline reduced the destruction of dopamine neurons, the brain cells that die in Parkinson’s patients. Other research found that the drug inhibited the misfolding of a protein in the brain called alpha-synuclein, a characteristic of Parkinson’s.

Collier is in the process of publishing his laboratory data, and he expects to skip the usual phase I clinical trial, since nortryptiline already has been proven safe and well-tolerated. That would mean the clinical trial could begin with phase II, shortening the period it would be under study with human patients. Meanwhile, he is continuing other studies, including into how the normal aging of the brain predisposes patients to Parkinson’s, Alzheimer’s and other neurological diseases.
Benjamin Combs obtained his bachelor’s degree in electrical engineering, but then his interest turned to a different kind of circuitry, specifically the short circuits in the human brain that cause neurological diseases, such as Alzheimer’s.

Since earning his doctoral degree in molecular, cellular and developmental biology, Combs has dedicated his career to understanding the causes of Alzheimer’s. His research focuses on the role of a protein called tau that is believed to be involved in the disease.

Tau plays an important role in a healthy brain, helping maintain the pathways between cells for normal brain function, but when tau becomes defective brain cells begin to die.

“There’s something good suddenly becomes bad,” said Combs, who works in a laboratory run by Nicholas Kanaan.

Previous research showed that in Alzheimer’s patients, the tau protein formed tangles, gumming up the works and appearing to cause brain cells to die. Combs and other researchers now believe that tau becomes toxic to brain cells even before the tangles are formed.

He compared the brain’s axons, the threadlike bodies that connect cells, to a railroad track.

“It seems that tau is involved in that process and in deciding when the train releases its cargo,” Combs said. When tau becomes defective, “it starts to release that cargo earlier and in the wrong place,” he said, “and the cell eventually dies. In order to stop that from happening, we need to figure out what’s happening.”

Knowing precisely when things go wrong can help researchers develop treatments to intervene at the right time and prevent or at least delay the onset of Alzheimer’s and other forms of dementia.

“The idea of a cure for Alzheimer’s disease is a long way away, but there are huge benefits to be made by delaying the onset,” Combs said. “If we could even find a way of delaying the onset of the disease by five years, that would greatly reduce the incidence,” in effect allowing many patients to outlive the disease.
Alzheimer’s is a complex disease that requires a multifaceted treatment plan. “The heterogeneity of the disease is what makes it so complicated to treat,” Scott Counts said. “What we’re looking for is not exactly a magic bullet, but a cocktail,” a combination of therapies to offset the sequence of neurological events that lead to Alzheimer’s.

He and other scientists know that many changes occur in a brain afflicted with Alzheimer’s. The challenge is in distinguishing those that are innocuous from those that cause the disease. Working with human brain samples and laboratory models, Counts has identified molecular pathways in the brain that appear to contribute to Alzheimer’s. The goal, he said, is to find new therapies to target those pathways, shutting down some that appear to be causative and turning on others that appear to protect brain cells.

One pathway, for example, that is supposed to remove a protein called tau when it forms into clumps and becomes toxic tends to be turned off in Alzheimer’s patients, allowing tau to accumulate and cells to die, he said.

Another area of his research is into the “selective vulnerability” of brain cells—why some associated with cognition die, while others, such as those that control muscle movement, survive. “The idea,” Counts said, “is to figure out why those neurons crash and burn while others stay healthy.”

With blood samples from Alzheimer’s patients, he and colleague Irving Vega are looking for biomarkers that might allow physicians to diagnose Alzheimer’s earlier and begin treatment before symptoms appear. Counts is also heading a plan to create a “brain bank” of tissue samples that could provide researchers with a wealth of information about Alzheimer’s and other neurodegenerative diseases, a joint project of Michigan State University and Mercy Health Saint Mary’s.

“To me, dementia always has been fascinating… trying to find ways to prevent this disconnection is what really drives me.”
It is a disease most commonly associated with the elderly, yet exactly why age is a risk factor for Alzheimer’s remains unknown.

Based on her many years of research, Marcia Gordon believes the body’s immune system contributes to the neurodegeneration. Studies have shown that the buildup of two proteins in the brain – beta amyloid and tau – is associated with Alzheimer’s.

“The brain tries to correct for that,” triggering an immune response and inflammation, Gordon said. In her laboratory, she has experimented with blocking the inflammation to see how it affects the buildup of tau, which is believed to cause the death of brain cells in Alzheimer’s patients.

After years of research at the University of South Florida, Gordon and her husband, David Morgan, are joining the growing number of College of Human Medicine researchers studying the causes and seeking better treatments for neurodegenerative diseases, including Alzheimer’s and Parkinson’s.

Gordon’s and Morgan’s research already has led to clinical trials of a vaccine and of antibody injections to counteract the buildup of beta amyloid, which begins accumulating in patients’ brains long before symptoms appear. They are researching another treatment they hope will reverse the effects of tau.

Currently there is no cure or effective treatment for Alzheimer’s, “but we’re very, very close,” Gordon said. “Now we have the ability to look inside the human brain (with a PET scan) and see if a patient has an accumulation of tau.”

Early diagnosis could allow physicians to begin treating the disease, thus delaying or preventing the onset of symptoms.

Joining the College of Human Medicine offers her the opportunity to work closely with other scientists studying Alzheimer’s, Parkinson’s and other neurodegenerative diseases, Gordon said.

“We’re starting to see that a lot of what we’re learning in one disease has application in the other disease,” she said. “We can work a lot faster and do a lot more if we interact and cooperate with each other.”
As an undergraduate, Nick Kanaan’s interest in psychology took an abrupt turn when a professor invited him to his lab and introduced him to Huntington’s disease, one of the many devastating neurological disorders. “It went from there,” Kanaan said. “I was totally captivated by aging and neurodegenerative research.”

Now armed with a doctoral degree in neurological sciences, Kanaan has dedicated his career to “understanding the molecular mechanisms that drive these diseases,” a prerequisite to developing better treatments. Much of his research is into a protein called tau, which is present in normal brains, but also appears to be a factor for many neurodegenerative diseases, including Alzheimer’s, frontotemporal dementia, traumatic brain injury and Parkinson’s. Long before symptoms appear, tau (rhymes with wow) forms into clumps and becomes toxic, causing brain cells to die, a condition called tauopathy.

“Our lab is aimed at targeting the toxic mechanism of tau,” Kanaan said. “Once tau is there, how can you stop it from doing what it’s doing?” One way is to manipulate or block the signaling pathway of tau, he said. In his lab, Kanaan also is developing “monoclonal antibodies” that hunt down and block the toxic forms of tau. These antibodies may prove useful as immunotherapies for diseases like Alzheimer’s.

One strength of the MSU researchers is that they work in close collaboration, sharing information while studying different aspects of neurological diseases. Irving Vega, one of Kanaan’s colleagues, for example, also is studying tau, but is looking for early biomarkers that could allow physicians to diagnose and begin treating Alzheimer’s before symptoms appear.

Although the work they do is highly complex, Kanaan’s reason for doing it is not. “The answer is kind of simple,” he said, recalling his first exposure to the human toll of neurological diseases when he was an undergraduate. “It really spoke to me,” Kanaan said. “You realize how devastating these diseases are. It’s about helping people. That’s what keeps us going.”
His early studies into the effects of the drugs cocaine and ecstasy on the fetal brain eventually led Jack Lipton into Parkinson’s disease research. The similarities are not as remote as one might think. “Originally, I was studying the development of dopamine neurons in fetuses and how they were affected by drugs like cocaine and ecstasy,” Lipton said, adding that it was his expertise in this area that led him toward the study of Parkinson’s disease in which dopamine neurons die in the brains of patients.

In addition to conducting his own research, Lipton chairs the Department of Translational Science & Molecular Medicine, which includes several teams researching Parkinson’s, Alzheimer’s and other neurodegenerative diseases. “As department chair I aspire to use my skills on behalf of my peers to help them become the best scientists they can be,” he said. “I do it as a service to my colleagues, my college and the community.”

Lipton currently is looking for new targets to promote the survival and regeneration of brain cells in Parkinson’s patients. He and colleague Nicholas Kanaan are studying an entire class of regeneration-associated genes, hoping to identify which ones can aid in the survival and regeneration of the brain cells that produce dopamine, a neurochemical that declines in Parkinson’s patients.

Under a process called gene therapy, they use altered viruses to over express candidate genes and silence others “so we can determine which ones are the key players and which ones are bystanders” in Parkinson’s disease, Lipton said. “It’s kind of like detective work. You put them all under a bright light and see what they say.”

He and colleague Irving Vega have recently been funded to develop a high-throughput screening to study how various combinations of genes interact to cause the survival or death of brain cells, a much quicker method than in the past when a researcher could spend 20 years studying the function of one gene.

“The goal with this project is to understand how genes interact to cause the disease without worrying about what each gene does,” Lipton said. “We may find there are several different combinations that cause Parkinson’s or Alzheimer’s.” The ultimate objective, he added, is to “better understand what causes disease so we can better treat it.”
To describe his cutting-edge research into gene therapy, Frederic Manfredsson often recalls an ancient tale from Greek mythology. Much of his work focuses on changing the genetic material in a common virus—the adeno-associated virus, or AVV—and introducing it into a patient to battle many diseases that have genetic components, including neurodegenerative diseases such as Parkinson’s disease. In scientific terms, AVV is a “viral vector.” Manfredsson called it “a biological Trojan horse.”

“You’re hijacking the virus,” he said. “You use the virus to carry in whatever genetic material you want.” The adeno-associated virus is present in a large portion of the population, but does not cause disease. In his Grand Rapids laboratory, Manfredsson removes 99 percent of the virus’s genetic material and replaces it with other genetic material. That technique has been used in clinical trials to successfully treat eye diseases and is being tested for efficacy in neurological disorders. Manfredsson is optimistic it also can be used for interrupting the biological processes that cause Parkinson’s by switching certain genes on or off.

“Can we go in and stop this process from happening?” he asked. “It’s a tremendous utility for a researcher. I can turn genes on. I can turn genes off. I can engineer new genes. The possibilities are endless.”

His research also focuses on the role of the protein alpha-synuclein, which, when it misfolds, is believed to cause neurons to die in Parkinson’s patients.

“We have to understand what makes a cell die before we can fix it,” he said. For many Parkinson’s patients, the disease not only attacks neurons in the brain, but also in the gastrointestinal track, causing constipation. Armed with two grants, Manfredsson and his colleague Matthew Benskey are studying what occurs to neurons in the colon that causes constipation.

“Ultimately, you want to have a treatment,” he said, “but you need to have the basic science to understand what that treatment will be. In the end, one can only hope that something good can come out of it for the patients.”
When it comes to treating Alzheimer’s disease, David Morgan suggested two possible approaches – one clearly better than the other.

“We could treat a person who already has Alzheimer’s disease,” he said, “but by then they’re already pretty far down the road.” A better approach, he said, is to diagnose Alzheimer’s in its early stages and stop it before the symptoms appear.

“The easiest way to cure any disease,” Morgan said, “is to prevent it.”

That’s why he has spent his career studying the causes of Alzheimer’s and looking for ways to intervene before it becomes the devastating illness that afflicts five million Americans and costs more than $250 billion a year. His research already has led to several clinical trials of treatments he believes could prevent full-blown Alzheimer’s.

After years of work at the University of South Florida, where he was director of neuroscience research, Morgan is bringing his expertise to the College of Human Medicine. His research – along with that of Marcia Gordon, his colleague and wife, who also is joining MSU – has led to clinical trials, first with a vaccine and now with antibody injections to activate the body’s immune response and stop the buildup of a protein called beta amyloid in the brain.

Morgan and Gordon are studying other possible therapies to prevent the buildup of a second protein called tau and to treat inflammation in the brain that accompanies Alzheimer’s. Together, beta amyloid and tau conspire to kill neurons in the brain, causing Alzheimer’s disease.

“Amyloid brings the neurons to the party,” Morgan said, “and tau kills them.”

Amyloid begins increasing in the brain 10 to 15 years before symptoms appear. Physicians could detect the buildup with a PET scan, spinal tap or even a simple blood test, Morgan said, allowing them to begin treatments to stop the disease.

“My feeling is that one of these (clinical trials) is going to give us the tools to prevent Alzheimer’s disease,” he said.
Aging is the most significant risk factor for developing Parkinson's disease. Ivette Sandoval wants to know why.

“I am developing a new line of research,” Sandoval said, specifically how aging affects normal cellular processes in the brain, leading to Parkinson’s disease. “If we manage to identify what it is that makes certain cells more prone to die,” she said, “then we might be able to identify some key biological processes that allow us to prevent or treat Parkinson’s, and possibly other neurodegenerative diseases.”

Her research uses epigenetics, the study of how diet, exercise, sleep, aging and other environmental factors cause chemical modifications in DNA, turning genes on or off. The Parkinson’s Disease Foundation awarded Sandoval a $100,000 postdoctoral fellowship to further her research. In Parkinson’s patients, some cells in the brain’s substantia nigra die, while others appear to remain healthy. What makes some cells more vulnerable to disease, Sandoval wondered, while others appear to remain healthy?

A protein called alpha-synuclein appears to play a role, but exactly how is controversial. Alpha-synuclein is the main component of Lewy bodies, or protein clumps, which are a characteristic of Parkinson’s disease.

“I’m looking at the interplay between alpha-synuclein and aging to try to understand the vulnerability of the cells that die in Parkinson’s,” Sandoval said. While her research is basic science, Sandoval looks forward to when it can help Parkinson’s patients.

“I think we have so much to learn,” she said, adding that “studying the epigenetic process will help us understand more.”

“I do love basic science,” she said. “We need to understand the basics, if we want to find cures and help people lead better lives. If that were to happen, I would be very, very happy.”
Caryl Sortwell, PhD
Professor & Associate Chair
Translational Science & Molecular Medicine

Caryl Sortwell wants to know why some Parkinson's disease patients don't respond as well as others to standard treatments.

For years, most Parkinson's patients have been prescribed levodopa, a synthetic drug to replace the brain's dopamine, a neurotransmitter that declines as the disease progresses. For some, the treatments worked pretty well; for others, not so well.

The reason, Sortwell believes, is that about one-third of Parkinson's patients have genetic variations that disrupts the release of a protein called brain derived neurotrophic factor (BDNF), which helps brain neurons survive and promotes the growth of new ones.

Sortwell studied many variants in the gene for BDNF variants and identified three that in Parkinson's patients are associated with a suboptimal response to levodopa. She is studying several other genetic variants that could affect how well Parkinson's patients respond to treatment.

The goal, she said, is to personalize each patient's care by identifying the genetic variants that determine what treatment is likely to be most effective. That approach would not cure Parkinson's, but would improve patients' lives by turning it into a chronic but manageable disease. Some patients might respond better to different drugs or drug combinations, Sortwell said. For others, deep brain stimulation surgery might be the best option.

"Ultimately, that would help doctors work with their patients to design a treatment plan that, hopefully, would help them outlive their disease," she said. Sortwell also has developed a laboratory model to study what causes alpha-synuclein - a protein in normal, healthy brains - to misfold and accumulate into clumps called Lewy bodies, which are characteristic of Parkinson's.

"I have always been fascinated with neuroscience... I realized that by focusing in this area I could have a direct impact on people's lives."
For some Parkinson’s patients, the side effects of the drug for treating it are as bad as the disease. Kathy Steece-Collier’s goal is to improve the effectiveness of Parkinson’s drugs while minimizing the side effects.

Parkinson’s disease is caused by the death of neurons in the brain that produce a chemical called dopamine, a neurotransmitter that is necessary for normal motor behavior. Too little dopamine causes the tremors and rigid muscles characteristic of Parkinson’s. But too much dopamine—sometimes induced by the anti-parkinsonian medication levodopa—can cause involuntary movements known as dyskinesia.

Why do some Parkinson’s patients develop dyskinesia, Steece-Collier wondered, while others don’t? As the neurons that normally produce dopamine die, other neurons that usually make another neurochemical called serotonin try to take up the slack by producing dopamine, she said. The problem is that the serotonin neurons release unregulated amounts of dopamine, which is thought to be one significant factor causing dyskinesia.

“Where my research comes in is in figuring out why some Parkinson’s patients have dyskinesia, and some patients are more resistant,” Steece-Collier said. The answer, she believes, lies in a protein called “nuclear receptor related 1,” or NURR1. Normally, NURR1 is thought to be repressed in a brain region called the striatum, Steece-Collier said, but when it is activated in this area, it appears to be associated with dyskinesia. Yet when activated in another area of the brain called the substantia nigra, NURR1 appears to protect the neurons that produce dopamine.

With a grant from the Michael J. Fox Foundation for Parkinson’s Research, Steece-Collier is studying the importance of suppressing NURR1 in the striatum while keeping it active in the substantia nigra, thus delaying the progress of Parkinson’s while avoiding dyskinesia.

She and colleague Frederic Manfredson, backed by a National Institutes of Health grant, are also researching genetic manipulation as a way of making neurons more receptive to drug treatment while preventing dyskinesia.

“If I can find a way to allow Parkinson’s patients to lead normal lives for much longer, that would be very rewarding,” Steece-Collier said.
By the time symptoms of Alzheimer’s disease appear, too much brain damage has been done already. That’s why Irving Vega is searching for early indicators of the disease so that new treatments can slow and possibly halt its progress before symptoms are developed.

“Right now, the field is trying to achieve two goals: early detection and treatment,” Vega said. “We know that neurodegeneration starts 20 or more years before clinical presentation. Thus, early detection is critical to effectively treat this terrible disease.”

Vega has identified several biomarkers that appear to be associated with the accumulation of a protein called tau, which is believed to be a factor in Alzheimer’s and other neurological diseases. One of those biomarkers shows up very early in the disease, he said, and even appears in cases of mild cognitive impairment, which often precedes Alzheimer’s disease.

“That biomarker—a type of protein—might protect brain cells from the toxic effects of tau, so this could be a target candidate that we need to find ways to activate early on,” Vega said. Treatments also could be developed to suppress one of the other biomarkers he identified to see if it reduces the accumulation of tau and, thus, slows the progress of Alzheimer’s.

For Vega, a native of Puerto Rico, the search for early signs and better treatments is driven in part by studies showing that Alzheimer’s occurs at a higher rate among Puerto Ricans, as well as other ethnic minority groups. The health disparities in Alzheimer’s disease are possibly due to the intersection between genetic factors and social determinants of health, such as socioeconomic status and education.

Such ethnic differences make it important to attract more minorities to medical research, Vega said, which is one of his professional goals.

“I believe that a treatment approach against a single target will not work with Alzheimer’s disease,” he said. “Ultimately, the goal is to develop a treatment regimen that targets key molecular pathways involved in the pathological process.”