After more than 20 years of arduous medical research on the neuroscience of Down syndrome, pioneering neurologist William Mobley two years ago achieved a stunning breakthrough at Stanford University. By coming up with a discovery that promises to make life better both for people with Down syndrome and Alzheimer's Disease, the internationally renowned neuroscientist has brought new hope to millions of suffering patients in this country and all around the globe.

By Tom Nugent, Photos by Nick Abadilla
When the breakthrough came in a neuroscience lab at Stanford University about two years ago, Dr. William C. Mobley (B.S. '70) was far too busy taking notes and planning new experiments to think about celebrating.

Instead of ordering in a bottle of French bubbly, Mobley (he has an M.D. and a Ph.D in neurology from Stanford) immediately redoubled his efforts to pinpoint the healing effects of a biochemical compound that his research team had just identified as “apparently very effective in reversing some of the brain deficits caused by Down syndrome.”

Mobley’s 2008 discovery has the potential to start making life better for millions of people with DS around the world in the future.

But it may also have a dramatic impact on 10-20 million Americans who are expected to be struggling with Alzheimer’s Disease in the next few decades, as 75 million members of the “baby boom generation” confront the health problems associated with aging. (Says the Chicago-based Alzheimer’s Association, which recently gave the former UNL chemistry-zoology major a $239,000 grant to continue his research: “The results of Mobley’s study could lead to new therapies for both Alzheimer’s Disease and Down syndrome.”)

What Mobley (pronounced MOB-lee) found in his Stanford lab on that morning could very well mark a turning point in the continuing struggle to tame two chronic degenerative diseases of the brain – by treating both people with Down syndrome and Alzheimer’s with a drug compound that replaces a key substance (norepinephrine) required for effective signaling between neurons.

The bottom line: Neurons (the information transmitting cells in the brain and nervous system) are connected quite closely to one another at a physical structure called a synapse. Each synapse is activated by a small neurotransmitter molecule that is released from one neuron to act upon its partner. All brain functions are made possible by the action of synapses, each of which serves a specific purpose. All losses of brain function are due to the failure of specific types of synapses. When neurons are damaged in degenerative diseases, synapses fail and the neurotransmitters used to communicate between neurons are unable to work. Mobley and his colleagues discovered that norepinephrine, a neurotransmitter required for helping the brain to learn and remember information, was deficient in a mouse model of DS. Deprived of this essential substance, the neurons could not communicate and cognition was compromised. The model organism mimicked what happens in elderly people with Down syndrome and in those with Alzheimer’s Disease who experience noticeable deficits in such basic functions as remembering and learning.

For Mobley and his colleagues at Stanford’s Department of Neurology and Neurological Sciences, the challenge had long been to find a way to reverse the harmful brain deficits of degenerative nervous system disorders like DS. Their approach was to first understand the genetics behind the ailments and then to seek therapies aimed at offsetting the damage they cause.

One way to do that, they reasoned, was to explore how another category of molecules might be affected in DS and AD. “Neurotrophic factors,” small proteins that normally signal to keep synapses active and healthy, might be involved in the degeneration of neurons in these disorders.
Mobley & Co. had been working for several years with a “mouse model” in which the presence of an extra copy of a specific segment of a mouse chromosome was used to “mimic” the neurobiology of humans with DS. Their challenging task: to see if they could learn from the model whether or not and how neurons were being deprived of neurotrophic factors and to prevent, at least partially, the expected loss of neurons.

For the Mobley team, the dramatic finding that neurotrophic factors were involved was announced by the clicking of a Geiger Counter-like device that was tracking a “radio-labeled” (radioactive) chemical marker in the lab test of the mouse brain cells under investigation.

“When I walked into the lab that day in 2002, I got a very nice surprise,” Mobley told Nebraska Magazine during a recent interview in the Department of Neuroscience at the University of California San Diego, which he now chairs. “All at once Jean Dominique, a talented ‘postdoc’ [post-doctoral researcher] hurried over and showed me the results of his assay of the neuron-signaling in the mice.

“Those results were clear and unequivocal – they showed that neurotrophic factors were involved in the degeneration of neurons. We went on to show that a specific gene was largely responsible for the problem, and we realized that we might very well be looking at a potentially important cause for both Down syndrome and Alzheimer’s.

“As it turns out, the brain chemistry in DS that causes the deficits is in many ways identical to the chemistry in Alzheimer’s, which is why virtually all people with Down syndrome also develop the brain changes of Alzheimer’s by the age of 40 or so.

“Because of the similarity, it was reasonable to expect that what we discovered about Down syndrome will also work to help Alzheimer’s patients.”

The next big breakthrough was in 2008. “We reasoned that the failure to communicate at synapses might be reversed by simply supplying the missing neurotransmitter,” Mobley explained. “Our focus was a population of neurons in the brain stem – i.e. those lying at the base of the brain – whose neurotransmitter is norepinephrine. The synapses that are activated by this neurotransmitter are very important for learning and memory, perhaps the most important ones of all in the brain.

“We discovered that in spite of the degeneration of the neurons that make this neurotransmitter, and the apparent decrease in the levels of this chemical at synapses, the synapses could still be activated in a culture dish if we artificially restored norepinephrine levels. My colleagues Ahmad Salehi, Alexander Kleschevnikov and Pavel Belichenko were very excited by this result. In studies in mice, we tested the idea that the same would be true in mice and found that it was. By giving the mice a drug that was converted to norepinephrine, we reversed some of the behavioral changes that affected them – changes that are similar to those in people with DS. The results suggested that we may be able to reverse cognitive problems in people with DS.”

Enormously encouraged by their finding, Mobley and his Stanford crew of investigators were also heartened by the fact that the compound they were studying has been studied for years in Japan and in other ongoing clinical trials by a U.S. company. Enormously encouraging to Mobley and his colleagues is that this company is now interested in trying out the compound in people with DS.

“The good news here is that we won’t have to wait through years of testing before moving the compound toward people with Down syndrome,” said the former UNl Phi Beta Kappa science student. “As a matter of fact, there is a strong interest in testing this compound as soon as possible. And that’s wonderful news for us in the lab – because our sole purpose right now is to help people with Down syndrome, and we’re hopeful we’re going to be able to do that sooner rather than later.”

So what was it like for Dr. M and his colleagues, when these breakthroughs occurred?

“You do get a warm feeling inside,” said the 61-year-old scientist with a cheerful smile. “But really, there’s no time to waste to follow up on the finding. What happens is that you immediately start asking yourself: How can we write this [experiment] up, in order to show exactly what we’ve found here? What are the scientific implications, and what further experiments can we conduct in order to better document the results?

“These moments of discovery are very nice, of course, but they don’t suddenly change everything. For me, scientific research is about working day in and day out in a really rewarding process with lots of joy in it. “I don’t see the process as one in which you do ‘years of grueling work’ and then enjoy a sudden breakthrough. I see it more as a matter of fully enjoying each and every day at work – and then also enjoying some special times [during breakthroughs] that are even better.”

Born in Lincoln to parents who were the descendants of English-German-Irish immigrants to Nebraska, Bill Mobley likes to joke that “my mother claims she was born [at what later became] the 50-yard line [of Memorial Stadium], a few years before it was built [in 1923]. I’m not sure that the 50-yard line claim is quite correct, but she was born in her parents house very close to the where the stadium would be built. Whenever I go to a game I try to think about what that spot must have looked like so many years ago.

“Anyway, we were dyed-in-the-wool Nebraskans, for sure. My dad delivered milk for Roberts Dairy for several years, and then he spent the rest of his career selling Butternut Coffee around Lincoln and all across southeastern Nebraska. He had grown up during the Depression, when money was extremely tight, so he hadn’t been able to realize his dream of going to medical school. But he was a very kind, thoughtful man who took good care of his five children and never complained. It was a deeply rewarding experience when I eventually completed my Ph.D and M.D. and become a neuroscientist.”

As a student at Lincoln’s Pius X Catholic High School, in the early 1960s, Mobley worked part-time as an orderly at Lincoln General ... and by the time he landed on the UNL campus in 1966, he was already determined to launch a medical career. After signing on as a member of the Sigma Phi Epsilon Fraternity (“One of my best memories of UNL is the camaraderie we enjoyed in the frat house”), he buckled down to some “very serious academics” ... and excelled in his coursework. He remembers working very hard in preparation for post-holiday final exams, sometimes studying for 120 hours or more for exams in organic chemistry.
LEADING THE WAY UP THE ‘MOUNTAIN OF HOPE’

By November of 2009, when he published his groundbreaking study for neuronal signaling in Scientific Translational Medicine (“Restoration of Norepinephrine-Modulated Contextual Memory in a Mouse Model of Down Syndrome,” http://stm.sciencemag.org/content/1/7/ra17.abstract), the relentlessly focused and apparently tireless researcher was convinced that the compound represented a “huge opportunity” to improve the lives of people with Down syndrome ... and perhaps also the lives of Alzheimer’s patients in the years ahead.

“If you ask me what we’re hoping to accomplish here at UCSD [in the Department of Neuroscience, which he began chairing last year],” he will tell you with a smile of quiet determination, “I would simply say that if we can help to make things better for a single person with Down syndrome, then all of our years of hard work will be fully justified.”

Optimistic and resolutely cheerful, Mobley said he’s convinced that medical research is well on the way to more breakthroughs in finding help for patients with degenerative diseases of the central nervous system. Still, he often frets over what he sees as the toughest problem now facing medical researchers in this country: “Finding ways to more effectively translate the discoveries of medical science to the clinic, where they can benefit patients, quickly and directly.

“This is an extremely difficult problem right now,” said the father of three now-adult sons (his wife of 38 years, Gretchen, is a retired nurse), “and it’s quite troubling that we can’t do a better job of getting new drugs and new therapies from the science lab out to the medical community in a reasonable amount of time.

“The obstacles in the way of translating great science to great medicine are so formidable that some of us have taken to calling the process the ‘Valley of Death.’ Right now the system is simply broken, that’s all. There are regulatory problems involved, and funding problems, and commitments of interest problems ... and the communications that go on between academia and industry simply do not work well. In the end, I believe that patients are suffering unnecessarily. We must get our act together – and now.”

Then, with a look of rock-solid determination and an enthusiastic nod of his elegantly groomed, silver-haired head: “What we have to do is to find a way to transform the Valley of Death into the Mountain of Hope, so that great science can more easily become great medicine!”

UNDERSTANDING DOWN SYNDROME
A Q&A With Pioneering DS Researcher William Mobley, M.D., Ph.D.

Q. What is Down syndrome and why is it called that?
A. Down syndrome is a developmental disorder that occurs because of a genetic mistake that takes place at the time of conception – i.e. when the sperm fertilizes the egg. The disorder causes an interruption in normal physical and intellectual development, and this leads to impairments of one kind or another after birth. The condition is named after Dr. John Langdon Down, the first physician to formally identify the disorder, back in 1866.

Q. What happens, exactly, to cause the disorder?
A. In essence, the genetic mistake is a failure to properly distribute the 21st chromosome to the egg (usually) or the sperm. This results in the presence in the fertilized egg of an extra copy of the 21st chromosome. All the problems that then are experienced by the embryo, the fetus, the child and the adult are due in one way or another to the presence of the genes on the extra copy of the 21st chromosome. These extra genes interfere with normal development of cells and tissues throughout the body and the nervous system. The interference leads to physiological abnormalities that produce both physical and mental deficits in people with Down syndrome.

Q. How many Americans are affected by Down syndrome?
A. The most recent estimates indicate that about one American infant in 800 is born with DS. About 5,000 children born in this country each year will have the disorder. At present, more than 400,000 people are living with Down syndrome in the United States.
Q. What are the physical symptoms?
A. Babies born with DS are often of small stature, hypotonic (i.e. with reduced muscle tone) and possess an unusual facial appearance with an upward slant to the eyes. They will often display a single crease in the palm of the hand, as well. Also, more than a third will struggle with DS-related heart defects of varying severity. But these symptoms vary a great deal. Most important, people with DS are nevertheless unique individuals and, like all humans, of inestimable value.

Q. What are the intellectual and learning deficits that can accompany DS?
A. Children with DS often struggle to keep up with their peers. They are slower than normal in learning to walk, talk and take care of themselves. The mental deficits they face can make it difficult to learn, but many do succeed in an ordinary school setting and go on to live rich and rewarding lives; they hold jobs and often live independently. Still, nearly half will require some level of assistance in their daily functioning while growing up, and some will need to live in a structured environment as adults.

Q. Are babies born with Down syndrome at greater risk for other diseases or physical disorders?
A. Yes. Children with DS are more susceptible to childhood leukemia and thyroid conditions, along with hearing and respiratory ailments. In addition, all will develop the brain changes of Alzheimer’s disease by age 40 and many will go on to show cognitive decline by the age of 60. Most of the medical issues can be treated with today’s powerful medications and therapies. It is the neurological issues, those involving the brain, that are the biggest concern at present. But even with these concerns, people with DS lead healthy lives with life spans that now average 60 years.

Q. Does the disorder strike babies regardless of race, ethnic background or economic class?
A. Yes. People of all races and economic status are affected equally. It’s also important to remember that Down syndrome is not caused by the behavior or lifestyle habits of the mother or father.

Q. Can people with Down syndrome learn to function successfully as adults contributing to their communities?
A. Absolutely. The majority of them will go on to lead rewarding, productive lives. But to accomplish that, they need what the rest of us need – warm, loving families and lots of support from parents, teachers, counselors and friends. It’s important to remember that people with Down syndrome aren’t really very different from those without DS. They want to get a good education and a good job. They want to date and enjoy an active social life. They face some special challenges, but none of us is without challenges in our lives.

Q. Is medical science helping to make life better for people with Down syndrome, and is there hope for an eventual cure?
A. I would rather speak of treatments than a cure. But there’s no doubt that bringing people with DS into the mainstream of society and advances in medical science have improved their lives enormously in recent years. Their life span has more than doubled in the past few decades. At my lab at the University of California San Diego, we’re very hopeful about the prospective treatments that could improve mental function. A major pharmaceutical company will soon began clinical trials of one such drug, and it is possible that it will be of significant benefit for people with DS. I’ve never been more optimistic about the future of DS research than I am right now. My colleagues and I are energized as never before to make a positive contribution to the well being of people with DS and their families.

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