A new study uncovers unprecedented evidence that Alzheimer’s disease might develop because a gene is missing.

The findings, published in *Nature* by Salk professor Tony Hunter and colleagues at Harvard University, mark one of the most significant genetic advances to date with Alzheimer’s disease. The research eventually might lead to new ways to prevent and treat this devastating condition.

The study showed that an enzyme named Pin1 (short for prolyl isomerase) is important for the normal function of nerve cells. Mice that lacked the Pin1 enzyme began developing nerve cell damage that is often seen in diseases like Alzheimer’s.

“When we first identified Pin1 in 1995, we knew that all animal cells had this enzyme and that it was likely to be important, but we had no idea that it would turn out to play a critical role in keeping neurons healthy in the brain,” said Hunter.

“Pin1 plays a pivotal role in protecting against age-related neurodegeneration,” said Harvard Medical School professor Dr. Kun Ping Lu. “This makes a convincing case that this enzyme should be taken into consideration in future studies of Alzheimer’s disease.”

Alzheimer’s disease is the most common cause of dementia in older people.

“This is an exciting advance in our understanding of neurodegenerative diseases,” said Hunter.
Alzheimer’s disease is the most common cause of dementia in older people. It affects about four million Americans.

It affects about four million Americans. As the current population ages, public health experts predict that the number of victims of the disease will increase significantly. There is no known cause, but autopsies of Alzheimer’s patients have shown tangles of proteins in the brain’s neurons.

The tangles, which contain a protein called tau, are string-like structures that appear abnormally bunched together in the brains of people who have died from Alzheimer’s. In healthy brains, tau helps give neurons their proper structure and function. In some diseases, including Alzheimer’s, tau changes its shape and becomes fibrous. The fibrous forms of tau clump together and eventually lead to nerve cell degeneration and dementia.

While scientists had assumed that this change in tau’s structure and function was due to the possible hyperactivity of a protein, this study showed the opposite: that a missing protein, Pin1, could very well be the culprit.

Salk Study Advances Understanding of Plant Genes and Their Function

Salk professor Joe Ecker and his team have one by one “knocked out” almost three-quarters of the genes in the genome of the model plant Arabidopsis, an accomplishment that will allow researchers to better understand how plant genes function.

“The information you get from the small mustard weed Arabidopsis is very likely to be immediately applicable to all plants,” said Ecker. “The information that we produce will be used by a range of people to improve plant growth, yield, and drought tolerance.” The findings were published in the August 1 issue of the journal Science.

Ecker was part of a multinational consortium that sequenced the genome of Arabidopsis in 2000. He emphasizes, however, that sequencing represents just the beginning of understanding how any organism functions. “Once the Arabidopsis genome was sequenced, we asked how many of the plant’s approximately 25,000 genes have been actually worked on. Less than 10 percent have been touched by any scientist,” he said.

The Salk researchers used a bacterium called Agrobacterium to disrupt the activity of genes. This is a process known as creating a gene “knockout.” The team was able to create gene knockouts in three-fourths (approximately 21,000 of 25,500) of all Arabidopsis genes, providing the largest collection of knockouts known for any higher multicellular organism. Turning a gene off allows researchers to understand its function.

“The availability of the complete genome sequence and new technologies have made possible what we believe is the definitive study of gene knockouts in Arabidopsis. These results provide significant new information in both the areas of functional genomics and basic plant biology,” said Ecker.

To share their findings with other researchers, Ecker and his team have developed a public database (http://signal.salk.edu). The database, containing more than 140,000 sequenced-indexed gene knockouts, is unprecedented for any model organism.
Gene Therapy Postpones Lou Gehrig’s Disease

Salk professor Fred H. Gage and his team have developed a unique gene therapy method that postpones the symptoms and nearly doubles life span in a mouse model of Lou Gehrig’s disease, which affects more than 30,000 Americans.

Lou Gehrig’s disease, or amyotrophic lateral sclerosis (ALS), is marked by the degradation of nerve cells that control muscle movement. It quickly attacks motor nerve cells in the brain and spinal cord, resulting eventually in paralysis and death. Its cause is unknown. While the disease was first identified in the 19th century, it gained international attention in 1939 when baseball great Lou Gehrig announced he had ALS and retired from the New York Yankees. He died two years later.

The findings are the first to show a significant degree of recovery after the crippling nervous system disorder begins and may lead eventually to a new, gene-based treatment for the disease. The study appeared in the August 8 issue of the journal *Science*.

Gage, Salk researcher Brian Kaspar, Jeffrey Rothstein, professor of neurology at Johns Hopkins University and their colleagues found that injecting a virus into muscles containing a gene that produces the nerve cell growth-stimulating protein called insulin-like growth factor-1 (IGF-1) resulted in longer life spans, preserved nerve cells and reduced muscle wasting.

“IGF-1 protein has been used in clinical trials for a while, with marginal results,” said Gage. “The biggest challenge has been to deliver the protein across the blood-brain barrier into the central nervous system. By injecting the virus containing the IGF-1 gene into muscles, the gene for IGF-1 reached nerve cells that controlled the muscle, resulting in the preservation of those nerve cells that would otherwise have succumbed to ALS.”

Gage and his colleagues found that delivery of gene therapy into muscle delayed the disease’s onset by 31 days and expanded the mice’s life span up to 265 days, compared to 140 days for the untreated mice. In addition to extending survival, the gene therapy treatment improved physical movement for the mice and increased their muscle mass by 20 percent.

The researchers demonstrated that IGF-1 triggers a molecular pathway that appears to preserve motor nerve function. When the receptor for IGF-1 is activated, an enzyme called Akt has a phosphate molecule added to it (a process called phosphorylation). The Akt enzyme is then activated and helps block the process of apoptosis, or programmed cell death.

While this research is still in the experimental animal stage and a number of steps need to be taken before any possible therapy is deemed safe and effective enough for use, researchers are in the planning stages of human trials for this gene therapy method.
Salk associate professor Ned Landau and his team have pinpointed how the body battles HIV, and this finding may lay the groundwork for new drugs to treat AIDS.

“What we have uncovered is a war that is being fought on the molecular level between viruses and cells. The war has been going on for millions of years, but we didn’t know about it until now,” said Landau. Their findings appeared in the July 11 issue of *Cell*.

“We have been focusing on an antiviral system that we never knew about — a single protein called APOBEC3G. APOBEC3G would be a powerful inhibitor of viruses such as HIV, except for one problem: the virus has outsmarted it. During the evolutionary war between the virus and the host, the virus developed an effective counter-measure.”

That counter-measure is a gene in HIV called virion infectivity factor (Vif). In an HIV-infected cell, according to Landau, Vif molecules are produced and then attach to the APOBEC3G protein molecules. Once attached, Vif prevents APOBEC3G from doing its job, and these viruses go on to replicate and spread throughout the body.

Having identified the interaction between Vif and APOBEC3G, Landau and his team then focused on a fundamental question: would it be possible to beat the virus at its own game?

“We found that mice also have APOBEC3G,” said Landau. “But interestingly, HIV can’t recognize the mouse protein. As a result, mouse APOBEC3G is a powerful blocker of HIV replication. The mouse APOBEC3G protein goes into HIV, and Vif can’t kick it out.”

The mouse APOBEC3G functions like a smart bomb with a time-delayed fuse. When the virus is produced in an infected cell, APOBEC3G molecules get into the virus. At first, the protein does nothing; however, when the virus infects a new cell, APOBEC3G is activated. As HIV begins to copy its genes into DNA, APOBEC3G attacks the virus, creating massive mutations. The viral DNA is so badly mutated that the viral genes can’t function.

“Drug companies may be able to use this information to design a novel type of drug to treat HIV infection. They could develop drugs that attach to APOBEC3G, physically blocking Vif from attaching. If Vif can’t bind to APOBEC3G, the process of HIV replication could be halted,” said Landau.

The study was funded by the National Institutes of Health, the Elizabeth Glaser Pediatric AIDS Foundation, Concerned Parents for AIDS Research and the James B. Pendleton Charitable Trust.
Ned Landau’s recent research on HIV received international coverage in July, with stories appearing in the San Francisco Chronicle, the Times of India, the San Diego Union-Tribune and Science Now. Landau’s lab identified a defense mechanism built into the virus and has uncovered one way the virus overwhelms human cells.

CNN’s nightly program Lou Dobbs Tonight interviewed Salk plant biologist Joe Ecker during a week-long series in July on the issues surrounding biotechnology and genetically modified food.

The San Diego Union-Tribune’s July 2 Quest section featured an article on the complex nature versus nurture debate. Salk professor Terrence Sejnowski said in the story that “your experiences with the world alter your brain’s structure, chemistry, and genetic expression, often profoundly, throughout your life.” Sejnowski also discussed this in his book Liars, Lovers, and Heroes, published in October 2002. Sejnowski appeared in the June 9 issue of Businessweek International. The article “What’s in a Face?” discussed our ability to read microexpressions to detect various emotions. Microexpression software has a variety of applications, including possible uses in airports to identify suspicious passengers.

The Dallas Morning News featured an article on July 7 that discussed the logical layout of the brain, focusing on the work of Salk professor Charles Stevens.

The New York Times discussed the cancer risks involved with gene therapy in an article on June 13. Salk associate professor Rick Bushman commented on the discouraging results of several studies, indicating a more prominent risk of cancer with gene therapy than originally thought.

The San Diego Union-Tribune featured an article on the UCSD Medical School commencement ceremonies, where Salk Nobel Laureate Sydney Brenner spoke to the graduates. Brenner was described as a 20th-century giant in genetics.

The Salk Institute held its first career exposition for postdoctoral researchers to learn how to get a job in today’s market. A story on the career expo ran in the San Diego Union-Tribune on June 4.

On June 5, Science Now included an article on Charles Stevens and Sunil Gandhi and their research on exactly how brain cells release neurotransmitters, the chemical signals nerve cells used to communicate with one another.
Dan Pankratz, a graduate student in Salk associate professor Susan Forsburg’s lab, has received a Blasker-Rose-Miah Fund grant from the San Diego Foundation. The grant will fund Pankratz’s last year of research as a student in the joint Salk/UCSD Ph.D. program. He works on checkpoint proteins and their role in meiosis — the process of creating germ cells.

Roger Guillemin was selected as one of fifteen inductees for the Hall of Honor. This honor is given for exceptional contributions to advancing knowledge and to improving maternal and child health. Guillemin will receive the award at the National Institutes of Health main campus in Bethesda, Md., on September 22.

Salk assistant professor Roland Riek has been selected as a 2003 Pew Scholar by the Pew Charitable Trust. The trust selected 20 junior faculty members at medical schools and research institutions, who will receive a total award of $240,000 to fund their research over a four-year period. The awards are granted to young scholars in basic and clinical sciences to encourage innovation in their research and to provide support as they establish their laboratories.

The National Institute of Child Health and Human Development (NICHD) has selected Salk Distinguished Professor Roger Guillemin as one of fifteen inductees for the Hall of Honor. This honor is given for exceptional contributions to advancing knowledge and to improving maternal and child health. Guillemin will receive the award at the National Institutes of Health main campus in Bethesda, Md., on September 22.
Francisco Navarro, who works with associate professor Ned Landau in the Infectious Disease Laboratory, was awarded $99,000 from the American Foundation for AIDS Research. He was one of 16 researchers worldwide who received a grant from the organization this year. The foundation is based in New York City and supports basic research aimed at combating HIV, the virus that causes AIDS. Navarro studies genes in non-human primates that either slow or stop the production of HIV. He plans to transfer these genes into human cells in the laboratory. He will also search for genes that enable human cells to resist the actions of HIV. These studies may help develop new therapies for the disease.

Paul Sawchenko, director of the Laboratory of Neuronal Structure and Function, was awarded a $3.3 million grant and the Jacob Javits Award from the National Institutes of Health (NIH) to identify how the immune and nervous systems interact to ward off disease. The research may result in treatments for such autoimmune diseases as multiple sclerosis and lupus. The cytokines, a class of chemical messengers secreted by cells of the immune system, cross the blood-brain barrier to exert their effects on the brain. The research may eventually result in a better understanding of how autoimmune diseases like multiple sclerosis and lupus arise, and may pinpoint cellular and molecular targets for developing treatments for these disorders.

Roland Riek
Francisco Navarro
Paul Sawchenko
Paul Slesinger

Paul Slesinger, an assistant professor in the Peptide Biology Laboratories, has received the 2003 Technological Innovations in Neuroscience Awards from the McKnight Endowment Fund for Neuroscience. Slesinger received the award for his work on understanding how the transmission of nerve impulses occurs when neurotransmitters bind to specific types of G protein-coupled neurotransmitter receptors (GPCR). He is developing a biosensor to enable neuroscientists to monitor changes in G protein activity noninvasively in real time during GPCR stimulation in neurons. A slow signaling pathway in the brain, GPCRs are involved in spatial learning and memory, among other neural functions. Slesinger received a McKnight Scholar Award in 1999 for his earlier research on G proteins.
Martin Hetzer, an assistant professor in the Molecular and Cell Biology Laboratory at the Salk Institute, focuses on how cells divide. Cell division is crucial to human development and is the sole way our genes are transmitted to descendants. Disruptions in cell division have been linked to many forms of cancer.

All human cells have a nucleus, which contains chromosomes that transmit genetic traits to further generations and control cell function. Hetzer is examining how the nucleus breaks apart during cell division and how it is reassembled correctly. Hetzer and his lab represent a growing research focus at the Salk investigating chromosome organization in dividing cells.

Jeff Long, who focuses on how embryonic plants organize themselves into “top,” “bottom” and “sides,” joins the Plant Biology Laboratory as an assistant professor. Long studies how young plants, particularly the common mustard weed Arabidopsis, develop one end that turns into roots and another that becomes the shoots. He also is studying how these plants then create specialized adult cells.

Long focuses on a series of genes, called TPL, that appear to help regulate the creation of roots and shoots. Mutations in these genes can cause plants to transform their shoot cells into roots. His studies will help plant biologists understand how to control plant growth and development, and could have implications for animal development as well.

John Young joins the Institute as a professor in the Infectious Disease Laboratory. He studies how viruses enter cells and take over the cells’ genetic machinery for their own reproductive purposes. He focuses on retroviruses like HIV — the causative agent of AIDS — that use their RNA to produce DNA that integrates itself into the host cell genome. His laboratory uses a virus called avian leukosis virus, or ALV, to study how retroviruses enter cells and cause disease.

Young also was the first to identify the cellular receptors for anthrax toxin, work that has implications for defending against bioterrorist agents. In addition to the anthrax toxin receptor, he has identified other cellular receptors that allow viruses to invade cells. He also is identifying proteins that enable viral genes to set up shop within cells.
**A New Taste for the Salk**

- If it’s Tuesday, could that mean it’s Cajun chicken day?
  
  The smells of hot sauce, garlic or simmering chowder emanate from the new Salk Institute cafeteria every day, drawing a near-capacity crowd for breakfast and lunch.

  The cafeteria’s new management began serving Salk employees and visitors May 1, and the number of customers has doubled in three months, says Executive Chef Dawn Tangeman. “We get in at 6 a.m., start serving breakfast at 7:15 and stay on through lunch,” she said. The staff has been involved with catered functions at the Institute, too.

  Tangeman, a graduate of the California Culinary Academy in San Francisco, came to the Salk after working for the W Hotel in San Diego and as a corporate chef. She’s backed up by staff who help with cooking, including Byron Wilson, a cook who graduated from the Culinary Institute of America.

  The cafeteria menu includes a range of cuisine for Salk employees, with an emphasis on healthy choices that incorporate fresh ingredients.

  “When I started, I spent a lot of time trying to find out what people would want,” she said. “I also cook food I like, and hope others like it, too.”

  Favorites have varied widely, though “soups always get good reviews. The lemon chicken with the artichoke-potato caserole; that was a good day.”

**Salk Hosts First Science Career Expo**

- The Salk Institute held its first Science Career Exposition on June 3, allowing Salk postdoctoral fellows and graduate students to network and make contacts within San Diego’s biotech community.

  Eighteen organizations, ranging from biotech companies including Illumina, Invitrogen, Gen-Probe and Neurocrine, to major pharmaceutical companies, public policy groups, academic institutions and law firms, came to the Institute to participate in the expo.

  Sophia Colamarino, a postdoctoral researcher in Fred Gage’s lab at the Salk, came up with the idea for the event, and worked with Beth Alton, the Institute’s human resources director, and Bruce Stevenson, vice president for academic affairs, to develop the program. Colamarino said the exposition focused on allowing postdocs and graduate students to learn job-seeking skills and explore “various career paths they may not have known existed.

  “There are so many seemingly minor points that make such a difference, like what to put on your résumé, how to structure it, how to dress for an interview, how to make a contact inside the company. For example, when you’re talking about your research do you say I or we?” Colamarino said.

  Chris Winrow, now a molecular neuroscience researcher at Merck, was a post-doctoral researcher at the Salk a year ago looking for a job. “I think a lot of companies have been spoiled because the talent pool here is so rich,” he said. “They become complacent, which is probably unwise. In six months, projects change and they could find themselves needing someone with a different skill set, and they missed the opportunity to make the connection here.”
Post-Polio Progress Reviewed

About 150 polio survivors and their supporters attended the Post-Polio Symposium at the Salk Institute in July.

The attendees heard a historic overview of the Salk Institute from Kathleen Murray, who was Jonas Salk’s assistant for the last five years of his life, and is now the assistant to Francis Crick, Renato Dulbecco, Sydney Brenner and Leslie Orgel.

Sam Pfaff, associate professor of developmental neurobiology, talked with the audience about the latest advances in basic research that may lead to new treatments for post-polio syndrome.

On the clinical side, Dr. Susan Perlman, director of the post-polio clinic at UCLA, discussed the options now available to patients with post-polio syndrome. About 40 percent of today’s 600,000 polio survivors in the United States suffer to some degree from the syndrome.

The Salk’s Triathlon Trio

Three scientists in the Systems Neurobiology Laboratories at the Salk Institute participated in a triathlon in September in Monterey, Calif., to raise money and awareness for the Leukemia & Lymphoma Society.

Leanne Chukoskie, Garth Fowler and Jon Shlens have been training for the past several months. Chukoskie is a postdoctoral fellow in the lab of Richard Krauzlis; her thesis work focuses on the integration of visual cues and motor function. Fowler, also a post-doc in the Krauzlis lab, focuses on the coordination of pursuit and rapid eye movements in target selection.

Shlens is a second-year graduate student in E.J. Chichilnisky’s lab. His work at the Salk focuses on understanding how the retina encodes sensory information in the visual system.

The Leukemia & Lymphoma Society is committed to attracting and funding outstanding investigators and research centers. The organization supports hundreds of researchers doing basic and translational research into cures for leukemia, lymphoma and myeloma.

Literary Agent Joins International Council

Linda Chester is a new member of the Salk Institute’s International Council. Chester is the principal of the Linda Chester Literary Agency, one of the country’s few bi-coastal literary representatives with offices in New York and California. She established the agency in 1988 in La Jolla and later opened the firm’s new headquarters in New York.

Chester represents author Wally Lamb and his two Oprah Club selections, She’s Come Undone and I Know This Much Is True; historian and novelist Janet Wallach, author of Chanel, Desert Queen; and Winston S. Churchill, Jr., grandson of Sir Winston, author of the upcoming Never Give In: The Best Speeches of Winston Churchill.

Members of the International Council act as informed ambassadors worldwide for the Institute. The council consists of approximately 90 members, who live in Europe, Asia and North America.

Council members include leaders in business and industry, medicine, law, finance, communications, the arts and community affairs.
Alzheimer’s disease and ALS are incurable neurodegenerative diseases that affect millions of people. Two recently published studies reviewed in *Inside Salk* provide novel insights into these conditions. The studies also illustrate two principles that have been embedded in Salk research for almost 40 years, namely that progress often comes through unpredictable routes, and that knowledge from one field of biology feeds into another.

A report in *Nature* from Kun Ping Lu’s group at Harvard Medical School and Tony Hunter’s lab at the Salk reveals new information about a protein whose absence may contribute to the pathology of Alzheimer’s disease. Pin1, an enzyme first discovered at the Salk by Tony and Kun Ping Lu in 1995, is present in all cells and facilitates the removal of phosphate groups from proteins, a process that regulates how proteins work in normal cells as well as in cancer. Cancer has been Tony’s primary interest, but this new work uncovers a function of Pin1 in nerve cells that may relate to Alzheimer’s.

Neuronal Pin1 regulates the function of a protein called tau, which is part of the micro-skeleton that determines the shape of nerve cell processes, like beams holding up the roof of a building. In mice lacking the gene encoding Pin1, tau ends up with too many phosphate groups, which causes the protein to change shape and form aggregates. These aggregates resemble the tangles surrounding dying neurons in the brains of Alzheimer’s patients. Aggregated forms of tau and of another protein, β amyloid, may be responsible for the nerve-cell death occurring in Alzheimer’s disease. Thus, Pin1 appears to be essential for keeping tau in its normal, unaggregated, non-toxic form.

In a study published in *Science*, Rusty Gage and his group, working with colleagues at Johns Hopkins University, exploited their earlier discovery that a virus called AAV injected into the muscles of mice is transported back into nerve cells of the spinal cord that supply the muscles. They applied this strategy to a mouse model of ALS (Lou Gehrig’s disease), a condition in humans in which nerve cells supplying muscle slowly die. When mice suffering from ALS were injected intramuscularly with AAV, genetically engineered to carry the gene for a growth-promoting protein called IGF-1, the virus slowed the progression of ALS and almost doubled the life span of the afflicted mice. IGF-1 exerts its effects by interfering with chemical pathways that kill nerve cells, pathways that were first discovered in the worm *C. elegans* through the Nobel Prize-winning work (2002) of the Salk’s Sydney Brenner, John Sulston, and Robert Horvitz. More studies are needed, but the Gage report suggests, for the first time, a treatment strategy that may be useful for mitigating the human form of ALS.

In providing important new information about Alzheimer’s disease and ALS, the Hunter and Gage studies embody a third principle of Salk science: basic research investigating the biology of cells inevitably leads to knowledge about human diseases that is essential for their solution.
The Salk Family Picnic drew several hundred faculty, staff, family and friends on a sunny August afternoon. The annual event, with an Australian theme this year, featured wave slides and bounce houses, activities for children and food, refreshments and an opportunity to catch up with colleagues and friends.