



SALK INSTITUTE
FOR BIOLOGICAL STUDIES



STORIES OF DISCOVERY

ALZHEIMER'S DISEASE RESEARCH

at the SALK INSTITUTE

INTRODUCTION

If, in the end, we are the sum of our memories and experiences, then Alzheimer's disease acts as a great eraser, wiping out who and what we are. First described by German psychiatrist Dr. Alois Alzheimer in 1906, the brains of Alzheimer's patients are riddled with amyloid plaques and neurofibrillary tangles. Finally, after decades of research, scientists at the Salk Institute and elsewhere have gained insight into the molecular basis of this devastating disease.

Salk professor Dr. David Schubert was among the first to study the biological functions of beta amyloid, the major constituent of the plaques. Since then, Salk researchers have made progress explaining how the toxic protein clumps form and they have developed gene therapy models in mice that appear to reverse the formation of these plaques. They have also discovered that our brain can sprout new neurons throughout life and coax stem cells to mature into new brain cells.

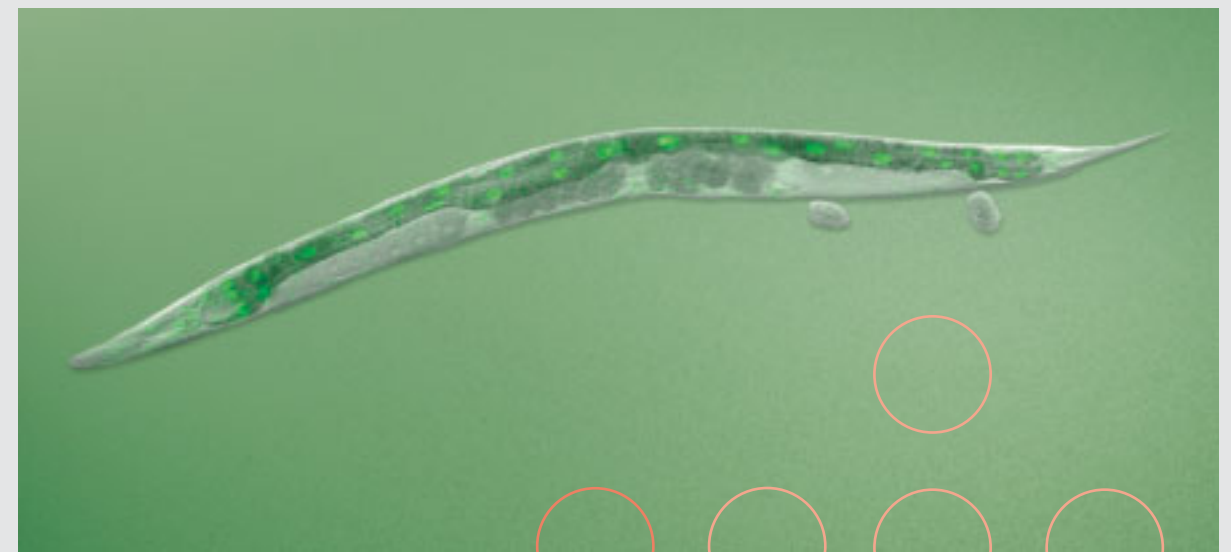
Today, Salk faculty members from various fields of science steadily chip away at the mystery of Alzheimer's disease and continue to provide hope through basic research.

Here are some of their stories.



BETA AMYLOID AGGREGATES FORM AS A SIDE EFFECT OF THE AGING PROCESS

Like most neurodegenerative diseases, Alzheimer's disease usually appears late in life. This raises the question whether Alzheimer's is a disastrous side effect of the aging process itself or whether it just takes a long time for the characteristic abnormal plaques to form in the brain. To find out, Dr. Andrew Dillin and his team employed the help of tiny Methuselah worms that—despite their advanced age—still have a youthful spring in their crawl. These indefatigable creatures proved that slowing down the aging process also reduced the formation of toxic beta amyloid aggregates. Dr. Dillin discovered that beta amyloid aggregates started to form in aged worms when their cellular detoxification machinery could no longer keep up. This insight may point scientists in new directions to develop drugs for the treatment of Alzheimer's and other neurodegenerative diseases.



OLD BRAINS, NEW TRICKS

LET'S TALK

MENTAL AND PHYSICAL EXERCISE ALIKE REJUVENATE THE BRAIN

Just about everybody assumed that we are born with all the brain cells, or neurons, we will ever have. Then Dr. Fred H. Gage and his team came along and toppled this long-held belief with a groundbreaking experiment that showed human brains sprout new neurons throughout life, particularly in the hippocampus — the brain's learning and memory center. The exact function of these newcomers is still unclear, although a few studies have linked them to the beneficial action of certain anti-depressants as well as to learning and memory.

Dr. Gage also discovered that physical activity such as running boosts the number of new neurons and improves learning and memory in mice, even elderly ones. Today, neurobiologists no longer argue about whether the brain can grow new cells. Instead, they are trying to

harness the brain's capacity to sprout new cells from its reserve of stem cells in order to treat disorders ranging from Alzheimer's and Parkinson's to depression.



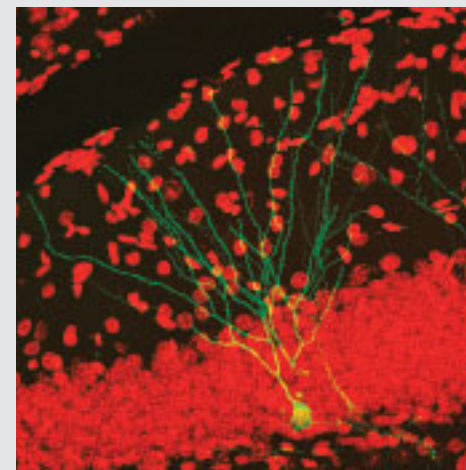
WHEN SCIENTISTS MEET, NEURONS FIRE AND SPARKS FLY

Jonas Salk believed that getting scientists to talk with each other would spark great ideas, and so does John Adler, a longtime member of the Salk Institute's Board of Trustees.

To foster communication between Alzheimer's disease researchers, he initiated, funded, and ultimately endowed an internationally renowned Alzheimer's symposium. For the last 15 years, nearly 50 scientists from around the world who are interested in topics related to the brain and Alzheimer's disease have been congregating annually at the Salk Institute to bounce ideas off one another.



Dr. Fred H. Gage (left) and Mr. John Adler



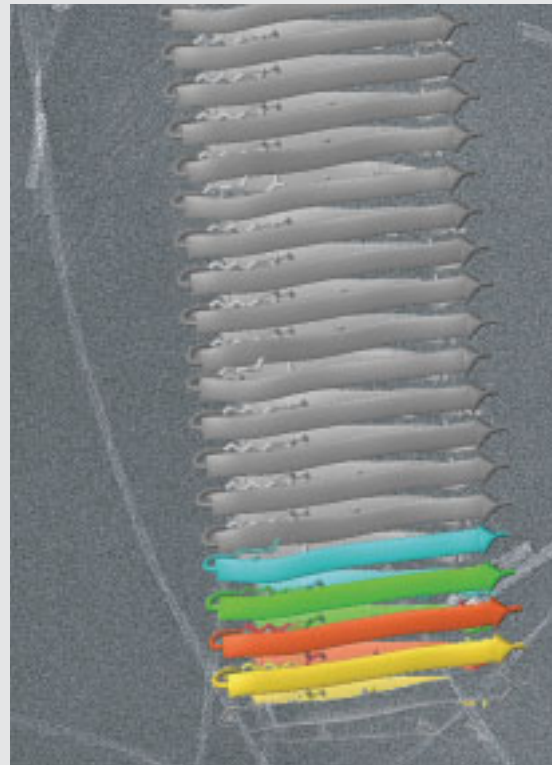
During one of these gatherings, two regular attendees were discussing Dr. Gage's discovery and decided to take it one step further. Hoping that mice prone to Alzheimer's disease would benefit from boosting the numbers of new neurons, they raised mice bred with an Alzheimer's gene in an enriched environment—large cages filled with running wheels, colored tunnels, and playmates. Mice living in the deluxe setting took almost twice as long as their counterparts living in bare standard cages to develop symptoms of

Alzheimer's disease. "Enrichment" via physical and mental exercise is now a key tool in the treatment program for Alzheimer's disease at leading health organizations, proving the power of communication.

FATAL ATTRACTION

A SHAPE CHANGE PRECIPITATES TOXIC PROTEIN AGGREGATES

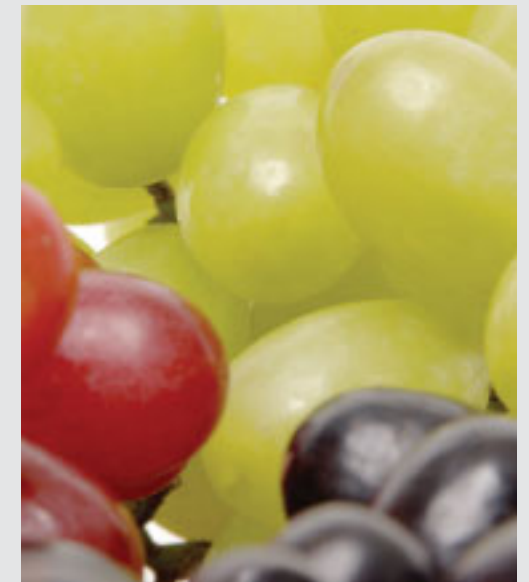
Clumps of abnormal protein that the brain cannot dispose of are at the heart of many, if not all, neurodegenerative diseases. Masses of the beta amyloid protein form the “senile” plaques seen in Alzheimer’s disease; prion protein deposits cause the brain’s severe destruction that characterizes “mad cow disease”; and alpha synuclein aggregates are associated with Parkinson’s disease. Dr. Roland Riek and his colleagues discovered that this motley group of proteins shares a common capability: They all can flip from a rather flexible and fully functional shape to a rigid, pleated structure called a beta sheet. Irresistibly attracted to each other, these beta sheets stack up like empty egg cartons, precipitating a chain reaction that causes toxic protein aggregates to form. Further Salk Institute studies to understand this transformation process will have a profound impact on explaining the underlying mechanisms of these disorders, as well as on efforts to develop novel therapies to treat them.



SWEET DEFENSE

UPPING SUGAR CONSUMPTION PROTECTS THE BRAIN AGAINST ALZHEIMER'S PLAQUES

The telltale plaques that pepper the brains of Alzheimer’s patients consist mainly of the beta amyloid protein. Although the production of beta amyloid occurs in everyone, healthy brains are able to clear away excess amounts. Accumulation of the toxic protein, however, stimulates the production of free radicals, oxygen-containing molecules that attack many of the cell’s major components. At high levels, free radicals can kill brain cells altogether. But not all brain cells in Alzheimer’s patients die.



Dr. David Schubert and his team discovered that many cells survive the same toxic conditions that kill their neighbors. He found that low amounts of beta amyloid increase the brain’s consumption of glucose, a form of sugar. Increased glucose metabolism aids the production of scavenger molecules that “soak up” free radicals and render them harmless. Thus protected, the cells can withstand the onslaught of high amounts of beta amyloid. Understanding how the brain protects itself against oxidative stress provides scientists with a way to possibly manipulate this biological process as a means of therapy.

TAXI VIRUS

UNTANGLING ALZHEIMER'S

GENE THERAPY REVERSES COURSE OF ALZHEIMER'S DISEASE IN MICE



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Many devastating diseases such as cystic fibrosis, muscular dystrophy, and sickle cell anemia can be traced to a defect in a single gene. Curing the disease by replacing the afflicted individual's defective gene with a correct copy is the elegantly simple promise of gene therapy. Dr. Inder Verma and his colleagues pioneered the use of stripped-down versions of viruses, particularly HIV, to taxi the much-needed genes to cells throughout the body and permanently insert them into the cells' DNA code.

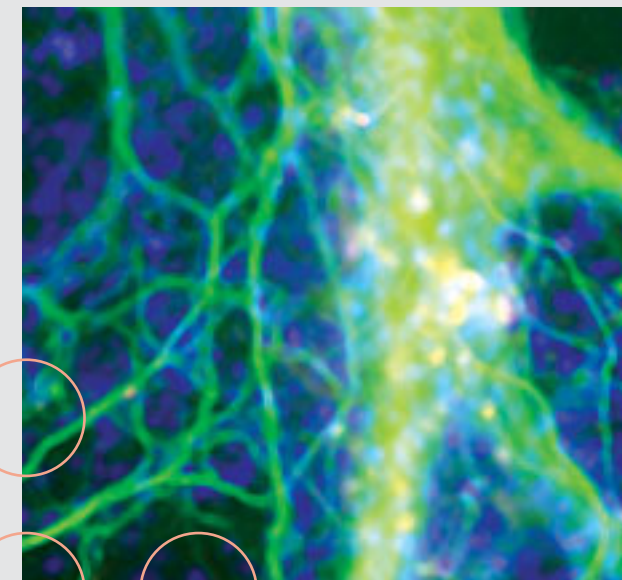
Dr. Verma successfully extended the use of gene therapy to mice that had been genetically engineered to develop Alzheimer's. His taxi virus successfully ferried neprilysin, an enzyme that has the ability to degrade beta amyloid, into the mice's brain cells. In a radically different approach, he was able to reverse the rodents' memory loss by silencing—instead of adding—an enzyme that is crucial for the development of Alzheimer's disease. Currently, Dr. Verma and his team are hard at work to perfect their techniques in mice, hoping to soon be able to test their approach in monkeys.

Brain Changes of Brain Slice by Jannis Productions: Rebekah Fredenburg, computer animation; Stacy Jannis, illustration/art direction.

A VERSATILE ENZYME RESTORES THE SHAPE OF A KEY PROTEIN

Dr. Tony Hunter and his team identified human enzyme Pin1 when they fished for proteins that play a role in the regulation of cell division in the obscure mold *Aspergillus nidulans*. They quickly established that Pin1's job is to latch onto other proteins when phosphates are added to flip their shape. But little did the team know that they had hooked a versatile, all-round talent that plays a central role in driving cell proliferation and preventing age-related neurodegeneration.

Blocking Pin1 kills cells as they attempt to divide, and several drug companies are already searching for substances that turn off Pin1 and wipe out fast-dividing cancer cells in the process. But in the manner of a true Jack-of-all-Trades, Pin1 can also restore the normal shape of tau, the protein that forms the knotty tangles that skew the communication



between brain nerve cells in Alzheimer's disease patients. In a new twist, Pin1 may also slow the production of plaque-forming beta amyloid and prevent its aggregation. These findings are an important step toward understanding the molecular mechanisms underlying the development of Alzheimer's disease and may help in the quest for effective treatments.

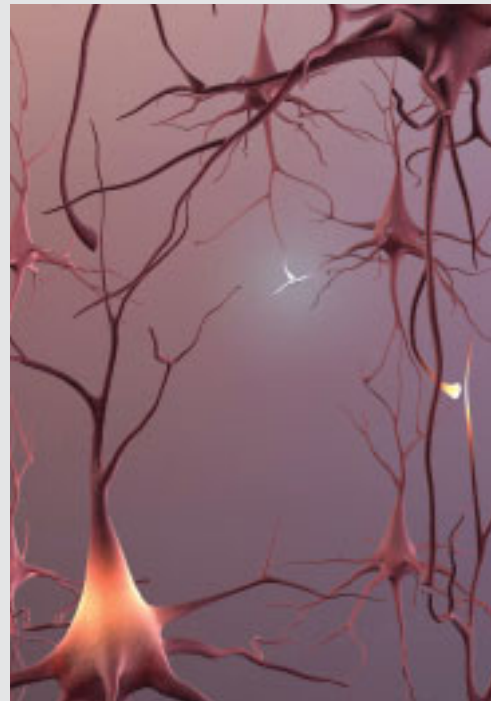
COMMUNICATION BREAKDOWN

CAREER DECISIONS

A BETA AMYLOID FRAGMENT INHIBITS COMMUNICATION BETWEEN BRAIN CELLS

Memory deficits and the loss of connections between brain cells precede the visible damage that ravages the brains of Alzheimer's patients in latter stages of the disease. This finding provoked scientists to ask new questions about the disease: What if it is caused by defective synapses—the specialized communication interfaces between neurons—and dying brain cells are just the result of gummed-up connections? This new concept led Dr. Stephen Heinemann to study the communication between nerve cells in mice that overproduce a mutant form of the human amyloid precursor protein (APP) from which a number of smaller fragments, one of them known as beta amyloid, are cleaved off.

He and his colleagues discovered that the transmission of signals between brain cells in these mice is severely hampered long before the first signs of toxicity and cell death appear. The interrupted cell-to-cell communication could explain the loss of memory that is apparent in early stages of the disease. On closer inspection, Dr. Heinemann discovered that a short APP fragment may be the culprit. Blocking the cleavage of APP should stall the progression of the disease or even make it possible to recover lost memory function.

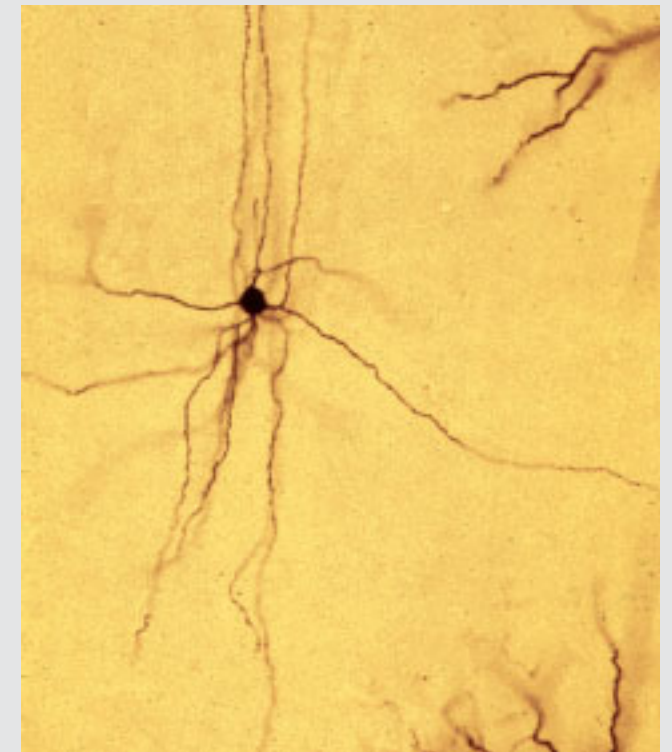


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The Neuron Forest by Jannis Productions: Rebekah Fredenburg, computer animation; Stacy Jannis, illustration/art direction.

FOR NEURONAL STEM CELLS, LOCAL ENVIRONMENT FUNCTIONS AS GUIDANCE COUNSELOR

Several years ago, Dr. Fred H. Gage's discovery of brand new nerve cells, or neurons, in the brains of fully grown humans flew in the face of conventional wisdom. Perhaps even more exciting was the finding that the source of these new cells was brain stem cells—unspecialized progenitors with the ability to morph into any type of brain cells. To tap their full potential, adult stem cells in the brain and elsewhere require additional nudging by their neighboring brain cells to turn into fully specialized cells. Dr. Gage and his team identified a crucial cellular signal, the *wnt3* molecule, that controls whether a stem cell becomes a neuron. Identifying the molecular instructions that push neuronal stem cells down a certain path of specialization is a first step toward generating the exact cell types needed to replace brain cells damaged by traumatic injury or degenerative disease such as Parkinson's, Alzheimer's, stroke, and epilepsy, as well as depression.



SALK FACULTY

CURRENT SALK FACULTY MEMBERS WHOSE RESEARCH IS RELATED TO ALZHEIMER'S AND OTHER NEURODEGENERATIVE DISEASES:



DR. ANDREW DILLIN, *Assistant Professor and Pioneer Developmental Chair, Molecular and Cell Biology Laboratory*

Dr. Dillin focuses on aging and neurodegeneration, using the worm *C. elegans* as a research model. Further elucidating the process of aging in this simple organism will lead to a better understanding of human diseases associated with aging, such as cancer, diabetes, and neurodegenerative diseases.



DR. FRED H. GAGE, *Professor and Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases, Laboratory of Genetics*

Dr. Gage concentrates on the adult central nervous system and the brain's unexpected adaptability to environmental stimulation that remains throughout the life of all mammals. His work may lead to methods of replacing or enhancing brain and spinal cord tissues lost or damaged as a result of neurodegenerative diseases or trauma.



DR. STEPHEN HEINEMANN, *Professor, Molecular Neurobiology Laboratory*

Dr. Heinemann studies the molecular details of communication among brain cells. Since neurological ailments such as Alzheimer's and Parkinson's, drug addiction, and mental disorders such as depression and schizophrenia are fundamentally disorders of brain cell communication, his research will provide new insights into the treatment of these disorders.



DR. TONY HUNTER, *American Cancer Society Professor, Molecular and Cell Biology Laboratory, Dulbecco Laboratory*

Dr. Hunter studies how cells regulate their growth and division, and how mutations in genes that regulate growth lead to cancer.



DR. ROLAND RIEK, *Associate Professor and McLoraine Chair in Neurobiology, Structural Biology Laboratory*

Dr. Riek studies protein structures, particularly the steps that occur when proteins misfold. Such misfolding problems can result in malfunctions in the cellular machinery, including Alzheimer's disease and transmissible spongiform encephalopathy, which includes the so-called "mad cow disease."



DR. DAVID SCHUBERT, *Professor, Cellular Neurobiology Laboratory*

Dr. Schubert studies hormones and other substances that affect the activities and survival of brain cells. Much of his research is providing new insights into Alzheimer's disease and other degenerative brain disorders.



DR. INDER M. VERMA, *Professor and American Cancer Society Professor, Laboratory of Genetics*

Dr. Verma is developing carriers for gene therapy. Replacing faulty genes with normally functioning genes provides a way to fix a problem at its source and treat hereditary diseases and cancer.



SALK TODAY

Perhaps no other condition robs its victims of their sense of identity the way Alzheimer's disease does. As the average age of the U.S. population climbs, the number of people ravaged by Alzheimer's disease continues to rise. Half of all people who reach age 85 are likely to be affected by this devastating disease.

Basic scientific research is the key to both finding drugs to prevent Alzheimer's and possibly reversing its effects when caught early. Understanding the biological processes that trigger the disease is critical to developing effective therapies that will stop its progression or, better yet, prevent it altogether.



If you would like to learn more about Alzheimer's research conducted at the Salk Institute, please call the Institute Relations office at 858.453.4100, ext. 2062 or e-mail communications@salk.edu.



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Where Cures Begin.

