Salk Institute for Biological Studies
10010 N Torrey Pines Rd
La Jolla, California 92037-1002
Telephone: (858) 453-4100
www.salk.edu

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INSIDE SALK WINTER I 2025

SALK INSTITUTE FOR BIOLOGICAL STUDIES

WINTER I 2025

InsideSalk

THE FUTURE STARTS UPSTREAM

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ON THE COVER:

Salk's River of Life represents the stream of discoveries that emerge from our labs and contribute to humanity's growing body of knowledge. These foundational discoveries then fuel the translational, clinical, and pharmaceutical sectors, enabling new technologies and cures that drive science and society forward.

Gerald Joyce, MD, PhD
President

Michelle Chamberlain
Vice President, Advancement

Heather Buschman, PhD
Head of Communications

Amy Cao
Science Illustrator

Isabella Davis
Science Writer

Alex Endsley
Graphic Designer

Stephanie Harada
Manager, Digital Communications

Kathleen Hart
Communications Manager

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Communications Administrator

Oliver Yambao
Senior Graphic Designer

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DISCOVERIES

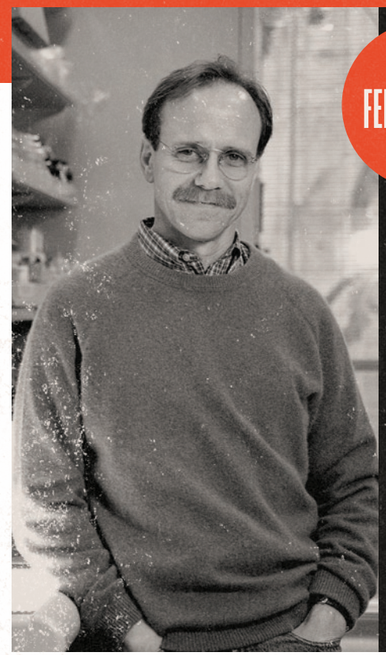
2000 TIME CAPSULE

A look back at 25 years of discovery

The clock strikes midnight, ushering in the year 2000. Salk researchers enter a new millennium of science. What questions will they ask? What answers will they find? On this night, they can only begin to imagine.

With each paper our scientists publish, they keep a record of the edge of knowledge. What did humanity know on this day? What mysteries were still left to explain? What new discovery can we now articulate for the first time?

In this special issue of our Discoveries column, we're cracking open the time capsule and revisiting three Salk studies from the year 2000. Let's see just how far we've come in 25 years and what our scientists are hoping to learn next.



SCIENCE

FEB 2000

Assessing the potential of mammalian neural stem cells

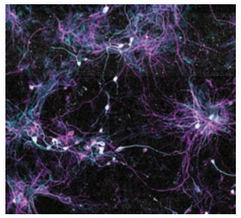
Salk neuroscientist **Rusty Gage, PhD**, recently became the first to show that the human brain can produce new neurons well into adulthood, overturning a century of scientific dogma that viewed the adult brain as fully developed and incapable of regeneration. However, the exact location and function of these adult stem cells have yet to be identified, and the molecular mechanisms that regulate them are still poorly understood. Here, Gage reviews the current state of the field and the possible future applications of neural stem cells in transplantation and regenerative medicine. Before the full potential of neural stem cells can be realized, he says, scientists need to learn what controls their development and what types of brain cells they can become.

TODAY'S REFLECTION

Gage's discovery of human adult neural stem cells was a landmark event in the history of neuroscience, forever changing how we think about the flexibility and regenerative power of the adult brain.

We've now learned where these stem cells are and what cells they can turn into. We're also getting a clearer sense of how diet, exercise, stress, and disease can influence adult neurogenesis, and how this affects our learning, memory, and mental health.

As scientists gained a deeper understanding of how stem cells turn into brain cells, an exciting opportunity began to emerge in the lab. Using these new insights, Gage's team developed methods to reprogram patient skin samples into various kinds of brain cells. Importantly, their methods were the first to produce neurons that maintain signs of a patient's age. This allowed researchers to create and study cell models of the adult human brain, revealing tons of new information about the biology of brain health, aging, and disease.



Gage's lab developed a technique to directly convert skin cells from older patients into aged brain cells, shown here.

These recent advances in stem cell biology are now enabling a new generation of neurotherapeutics, including improved strategies for stem cell transplantation and regeneration. Thanks to these decades of discovery, neural stem cells now hold significant promise for addressing neurological and neuropsychiatric disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), spinal cord injury, schizophrenia, and bipolar disorder.

> "The emergence of stem cell biology—the ability to shift the fate of cells from one lineage to another—has had a profound effect on our understanding of neurobiology and the development of novel therapies to treat neurological diseases." Rusty Gage

NATURE STRUCTURAL BIOLOGY JUN 2000

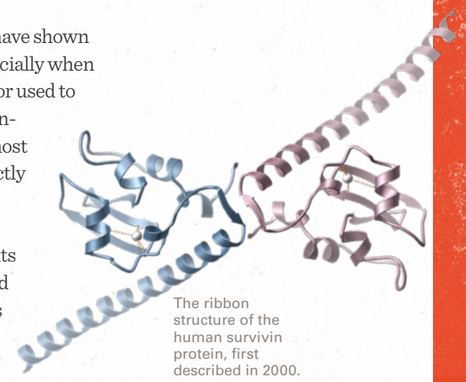
Cancer "survival" structure deciphered by Salk scientists

Cancer cells persevere against all odds, resisting death and continuing to grow, multiply, and invade the whole body. Salk scientists have now revealed the structure of a molecule responsible for cancer's tenacity, appropriately named survivin. Using X-ray crystallography, Salk scientists **Tony Hunter, PhD**, and **Joseph Noel, PhD**, discovered the 3D structure of the survivin protein, pinpointing the critical regions on its surface that are hot spots for driving cell division. Their findings could now support the development of new drugs to block survivin's cancer-promoting function.

TODAY'S REFLECTION

In the decades since Hunter and Noel first described survivin's structure, their discovery has been cited in hundreds of cancer biology studies, and interest in the molecule has grown tremendously. Survivin has now been implicated in nearly all forms of cancer and contributes to many patients' resistance to chemotherapy and radiation.

Several survivin inhibitors have shown promise over the years, especially when combined with other drugs or used to treat certain cancers like non-Hodgkin's lymphoma. But most drugs have struggled to directly block survivin's function, largely due to the molecule's unique structure. Knowing its detailed structure has helped explain these clinical results and guided scientists in more promising directions. The latest drugs use different strategies to target survivin and are making great headway in ongoing clinical trials.



The ribbon structure of the human survivin protein, first described in 2000.

2025 also marks Hunter's 50th anniversary at Salk. His discoveries have inspired hundreds of lifesaving cancer drugs, and his lab continues to characterize key cancer molecules that could serve as the basis for more precise and effective treatments.

"Methods for deciphering protein structures have advanced dramatically since the year 2000, with cryo-electron microscopy and predictive modeling programs largely replacing conventional crystallography. It's now much easier to learn the structure of a large protein or protein complex, which greatly facilitates the development of small-molecule drugs. Computer programs can now dock candidate drugs onto these 3D models and quickly identify those with the tightest fit, speeding up the process of cancer drug discovery."

TONY HUNTER

NATURE DEC 2000

Move over, Human Genome Project; plant biologists complete the first plant genome sequence

Arabidopsis thaliana, a small flowering mustard, has been the model research organism for plant biologists since the 1980s. Now, it's become the first plant to have its entire genome sequenced. Salk scientist **Joseph Ecker, PhD**, co-led the international Arabidopsis Genome Initiative and contributed the sequence for one of the plant's five chromosomes, while **Joanne Chory, PhD**, advised the national component of the project. The researchers are now part of a follow-up initiative aimed at deciphering the functions of the thousands of newly sequenced plant genes.

"In just 25 years, we've gone from sequencing a single plant genome to thousands. This has provided incredible insights into plant development, growth, and immunity. And now, thanks to these foundational discoveries, we can develop plant-based technologies that will help stabilize our environment and support food security for generations to come."

JOSEPH ECKER

Sprouting *Arabidopsis thaliana*.

TODAY'S REFLECTION

It's been 25 years since the first plant genome was sequenced, and the landmark paper has now been cited in over 10,000 subsequent plant biology studies.

After helping determine the DNA sequence of *Arabidopsis*, Ecker's lab successfully mapped the locations of all the individual genes and created mutations in each one. Other plant biologists were then able to order these mutants over email and use them to decipher the function of each gene.

The genetic tools and resources generated by the Arabidopsis Genome Initiative and the studies that followed it have completely transformed the field of plant biology. They also laid the groundwork for Salk's Harnessing Plants Initiative, which has now sequenced more than 900 additional plant genomes. Salk scientists are currently using this information to develop new varieties of wheat, rice, corn, and other staple crops with enhanced abilities to capture carbon, absorb nutrients, tolerate drought, and resist disease.

THE FUTURE STARTS UPSTREAM

Foundational discoveries are the source of tomorrow's breakthroughs, but what happens if we let the river run dry?

WHEN JONAS SALK DEBUTED THE FIRST EFFECTIVE POLIO VACCINE IN 1955, MANY ASSUMED HIS NEXT ENDEAVOR—THE SALK INSTITUTE—WOULD FOCUS ON VACCINE DEVELOPMENT. Instead, he designed the coastal campus to be a gathering place where the world's top scientists could study the fundamental mysteries of life. He knew the biggest scientific breakthroughs happen when researchers have the opportunity to work together and ask foundational questions.

> "We don't do science to make money. We do it to make discoveries, which we give back to society."
>
> GERALD JOYCE

This mission was embodied by one of the Institute's landmark architectural features, which he dubbed the River of Life—a stream that flows through the central Courtyard toward the horizon, where it appears to merge with the distant sea. It symbolizes the constant stream of discoveries flowing out of the Institute's labs and into humanity's greater body of knowledge.

Today, the River of Life is more than an inspiring symbol of Salk science; It's a powerful reminder of why foundational research deserves our support.

Salk is now one of the few institutions that remain fully dedicated to "basic science"—research that asks fundamental questions and generates foundational knowledge. In a healthy science ecosystem, this knowledge naturally flows into translational, clinical, and pharmaceutical sectors, enabling new technologies and treatments that improve our quality of life. Innovations like cancer immunotherapy, CRISPR gene editing, and GLP-1 weight loss drugs are now household names, but they all got their start as basic discoveries in a lab.

The issue is that science funding has increasingly prioritized the later stages of research and commercialization, leaving foundational science more vulnerable than ever.

"We don't do science to make money," says Salk President Gerald Joyce, MD, PhD. "We do it to make discoveries, which we give back to society. The insights we generate are what ultimately fuel the biotech and pharmaceutical industries. We need to replenish this river of knowledge or the whole ecosystem will run dry."