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THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

INSIDE SALK

Scientists activate dormant limb regeneration program in chick embryos

Chop off a salamander's leg and a brand new one will sprout in no time. But most animals have lost the ability to replace missing limbs. Now, a research team at the Salk Institute has been able to regenerate a wing in a chick embryo – suggesting that the potential for such regeneration innately exists in all vertebrates, perhaps even humans.

Their study, published on the cover of *Genes and Development* in November, demonstrates that vertebrate regeneration is under the control of the powerful Wnt signaling system. Activating Wnt overcomes the mysterious barrier to regeneration in animals like chicks that can't normally replace missing limbs, while inactivating it in animals known to be able to regenerate their limbs (frogs, zebrafish, and salamanders) shuts down their ability to replace missing legs and tails.

"In this simple experiment, we removed part of the chick embryo's wing, activated Wnt signaling, and got the whole limb back – a beautiful and perfect wing," said lead author, **Juan Carlos Izpisúa Belmonte**, professor in the Gene Expression Laboratory. "By changing the expression of a few genes, you can change the ability

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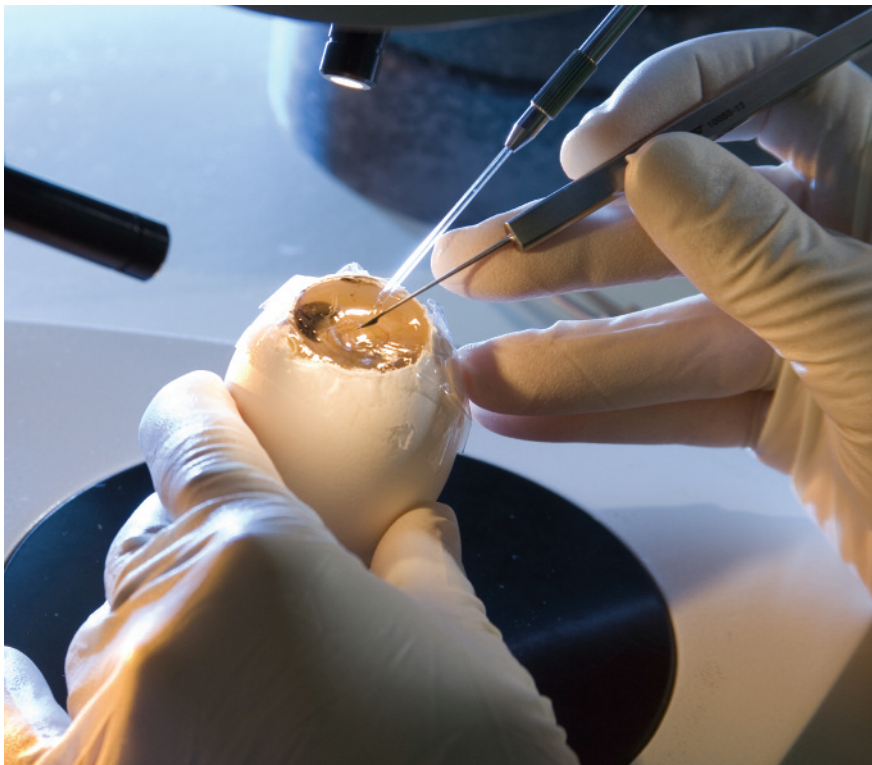


Performing their experiment on chick embryos, the Salk scientists first cut off the wing, then activated the Wnt signaling pathway to regenerate the limb.

of a vertebrate to regenerate its limbs, rebuild blood vessels, bone, muscles, and skin – everything that is needed."

This new discovery "opens up an entirely new area of research," Belmonte says. "Even though certain animals have lost their ability to regenerate limbs during evolution, conserved genetic machinery may still be present, and can be put to work again," he said. Previously, scientists believed that once stem cells turned into muscles, bone or any other type of cells, that was their fate for life. If those cells were injured, they wouldn't regenerate, but instead grew scar tissue.

Manipulating Wnt signaling in humans is, of course, not possible at this point, Belmonte says, but hopes that these findings may eventually offer insights into current research examining the ability of stem cells to build new human body tissues and parts. For example, he said Wnt signaling may push mature cells to go back in time and "dedifferentiate" into stem-like cells, in order to be able to then differentiate once more, producing all of the different tissues needed to build a limb.

"This is the reverse of how we are currently thinking of using stem cells therapeutically, so understanding this process could be very illuminating," he says. "Hypothetically, we could use the Wnt signaling pathway to dedifferentiate cells inside a body at the site of a limb injury, and have them carry out the job of building a new structure."

In 1995, the Salk researchers were first to demonstrate that they could induce the growth of extra limbs in embryonic chicks, and in 2001, they found that the Wnt signaling system played a critical role in triggering both normal and abnormal limb growth.

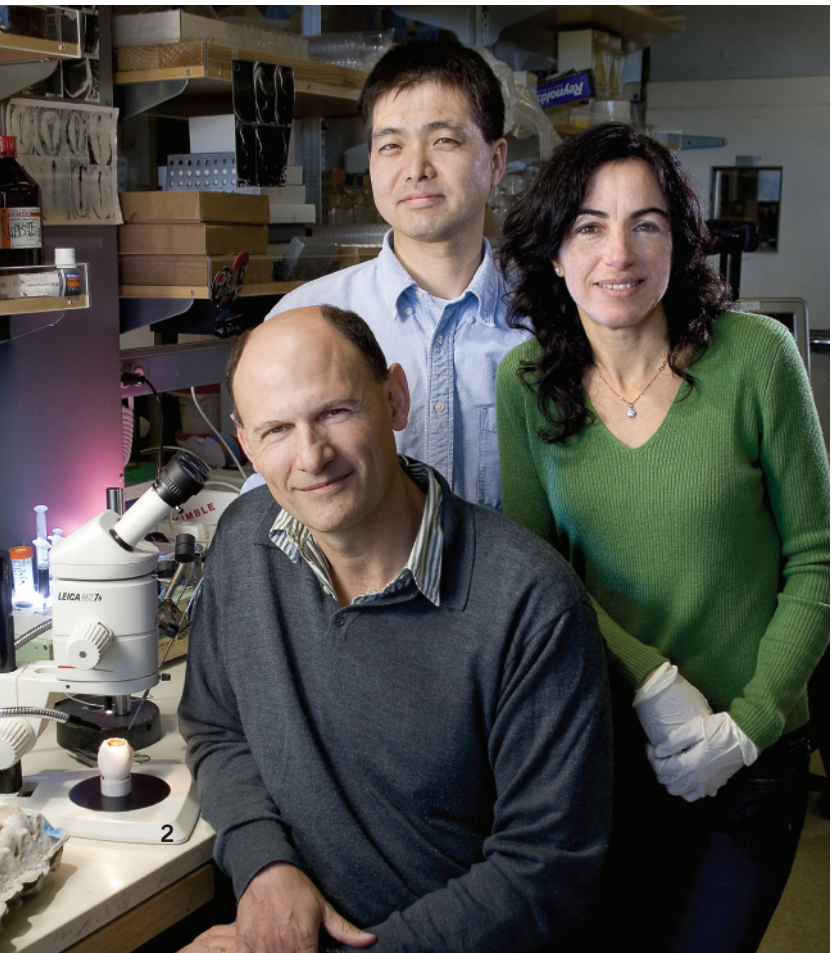
The current study was designed to see if Wnt signaling was also involved in the regeneration of limbs and included three groups of vertebrates: zebrafish and salamanders, which can regenerate limbs throughout their lives; frogs, which can only regenerate new limbs during a limited period during their fetal development; and chicks, which cannot regenerate limbs.

To manipulate animals' regeneration ability, the researchers used inhibitory and excitatory factors for Wnt signaling, which they delivered directly to the remaining bulge after they cut a limb from the experimental embryos.

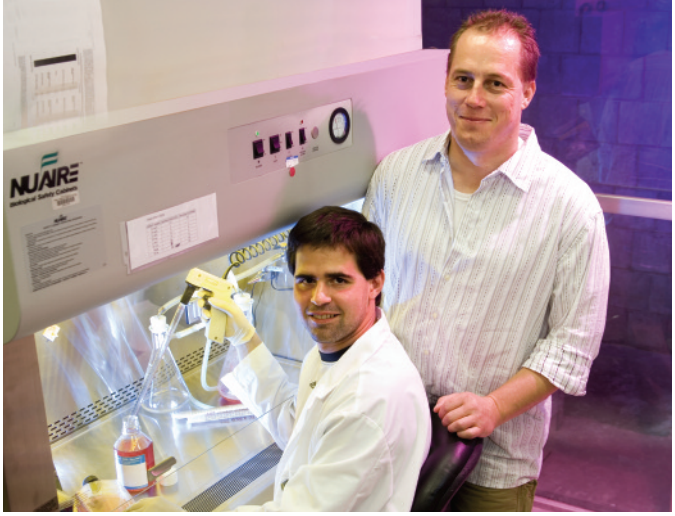
In adult zebrafish and salamanders, they found that blocking Wnt signaling with the inhibitory factors prevented normal regeneration. And, conversely, when they treated mutant adult zebrafish that cannot regenerate with the excitatory agent, the ability to regenerate fins was rescued, Belmonte says.

Using an inhibitory agent on frogs before the regeneration-enabled developmental window closed resulted in loss of that ability, but treating them with the excitatory agent after they had lost their regenerative capacity induced new limb growth.

They then performed the key experiment, successfully testing the ability of an excitatory factor to produce limb regeneration in chick embryos. The procedure was tricky, however. Belmonte noted that if Wnt signaling is activated for too long in these animals, cancer results.



Juan Carlos Izpisúa Belmonte (seated) with researchers Yasuhiko Kawakami and Concepción Rodriguez Esteban



Ramiro Verdun (left) and Jan Karlseder

DNA repair teams' motto: 'To protect and serve'

When you dial 911, you expect rescuers to pull up to your front door, unload and get busy – not park the truck down the street and eat doughnuts.

It's the same for a cell. Before dividing, the cell recruits protein complexes that repair breakage along the linear DNA chains. Without repair, damage might be passed on to the next generation of cells.

During a 2005 study, investigators at the Salk Institute observed that some of these cellular paramedics inexplicably idle at undamaged chromosome ends, known as telomeres.

The same team of researchers, led by **Jan Karlseder**, Hearst Endowment assistant professor in the Molecular and Cell Biology Laboratory, now reveals how in a study published in *Cell*. In doing so, they answer fundamental questions about how chromosomal stability is maintained.

Examining activity of telomeric and DNA repair proteins in cultured human cells, the investigators found that cellular repair proteins are recruited to exposed DNA ends right before cell division. But rather than fixing what resembles a break, the repair crew calls in a second conglomeration of repair proteins. This one, called the homologous recombination (HR) machinery, creates the essential protective structure at chromosome ends, or chromosomal cap.

However, at telomeres, just before they unload their cellular repair truck, HR crews apparently realize where they are – at the end and not the middle of the DNA strand – and reconfigure.

"At telomeres, they invade and then stop," says post-doctoral researcher **Ramiro Verdun**, lead author of both studies. "They adopt a different strategy."

That strategy is to tuck in the ragged chromosomal tips and form the cap, thereby hiding those tips from enzymes whose job is to reattach errant DNA strands. Telomeres assure chromosome ends remain intact throughout a lifetime of cell divisions. Erroneous fusion of chromosome ends leads to cell death and disease, Karlseder says. Almost all cancers show evidence pointing to telomere maintenance that has gone awry.

For nicotinic receptors, correct function depends upon their location

Location is of the utmost importance when finding a place to settle down. The same holds true for neurons. Researchers at the Salk Institute have revealed that nicotinic receptors, small molecules found on the surface of nerve cells, prefer distinct cellular subdivisions and have identified key elements that coax them into the right neighborhood.

The research team – led by **Stephen F. Heinemann**, professor in the Molecular Neurobiology Laboratory, and including first author Jian Xu and co-author Yongling Zhu – published its findings in the *Journal of Neuroscience*.

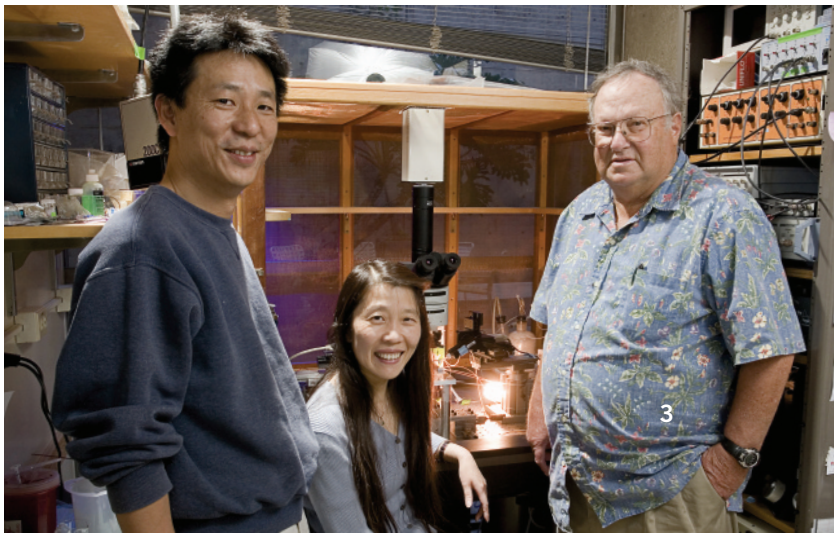
Nicotinic receptors are present on many neurons in the brain and nervous system and play an important role in many basic physiological processes and in diseases such as Alzheimer's and Parkinson's disease. Nicotine, the addicting substance in tobacco, acts through the same receptor.

Compared to other cells, neurons are highly polarized. They consist of a cell body, nucleus, and an electrically excitable output fiber, the axon, while incoming messages are received by dendrites. Within these two major compartments, specialized subzones and structures ensure the "multitasking" capabilities of individual neurons. Meanwhile, the precise location of neuronal proteins is critical for them to properly perform their designated tasks.

The researchers' findings demonstrated for the first time that two major types of nicotinic receptors are not distributed equally but follow distinct patterns. Different nicotinic receptors prefer different locations in neurons, suggesting that the two classes of receptors the researchers studied might each carry out different functions.

Through systematic screening, they identified two novel sequence motifs that are critical for directing nicotinic receptors toward either dendrites or axons, said Jian Xu, the study's first author.

"Ultimately, we are trying to understand how smoking may trigger addiction," Heinemann says. "Knowing where nicotinic receptors are located will undoubtedly help researchers uncover the initial reaction sites of nicotine inhaled through cigarette smoking."



Jian Xu (from left), Yongling Zhu and Stephen Heinemann

Natural chemical found in strawberries boosts memory in healthy mice

Pamela Maher

Fisetin, a naturally occurring flavonoid commonly found in strawberries and other fruits and vegetables, stimulates signaling pathways that enhance long-term memory, report researchers at the Salk Institute in the *Proceedings of the National Academy of Sciences*.

Pamela Maher, the study's lead author and researcher in the Salk's Cellular Neurobiology Laboratory, hit upon the beneficial effects of fisetin when she screened a collection of flavonoids, substances with anti-oxidant properties found in plants. She discovered that some of those compounds, including fisetin, induced differentiation or maturation of neural cells.

"That suggested to us that these compounds might be particularly beneficial, since they might not only protect neural cells from dying but might be able to promote new connections between nerve cells," Maher says.

Interestingly, the signaling pathway activated by fisetin in neural differentiation also played a role in memory formation, a process neuroscientists call "long-term potentiation" or LTP.

Together with co-authors Tatsuhiro Akaishi and Kazuho Abe, both at Musashino University in Tokyo, Japan, Maher tested fisetin's effects in a so-called object discrimination test in mice. The mice get to explore two objects for a certain amount of time before one of the objects is replaced with a new one the following day.

Mice that remember the object from the previous day will turn their attention to the new object. Indeed, mice administered a single dose of fisetin could better recall familiar objects.

"This is the first time that the function of a defined natural product has been characterized at the molecular level in the central nervous system and also shown to enhance both LTP *in vitro* and long-term memory *in vivo*," Maher says.

While eating strawberries sounds like an enjoyable alternative to popping a pill, Maher cautions that it would take about 10 pounds a day to achieve a beneficial effect.

More than meets the eye

If you have watched a jittery video, you understand the cinematographic task your brain is faced with. Our eyes constantly dart back and forth and we rarely hold still, yet we perceive our environment as stable.

Salk researchers recently showed in *Nature Neuroscience* that not only does the brain compensate for our flickering gaze, but it actually *relies* on eye movements to recognize moving objects.

"You might expect that if you move your eyes, your perception of objects might get degraded," explains **Richard Krauzlis**, associate professor in Salk's Systems Neurobiology Laboratory. "Nevertheless, you don't have the sense that the world has just swept across," he says. Instead the brain utilizes an image stabilization system to avoid perceiving the world as a blur.

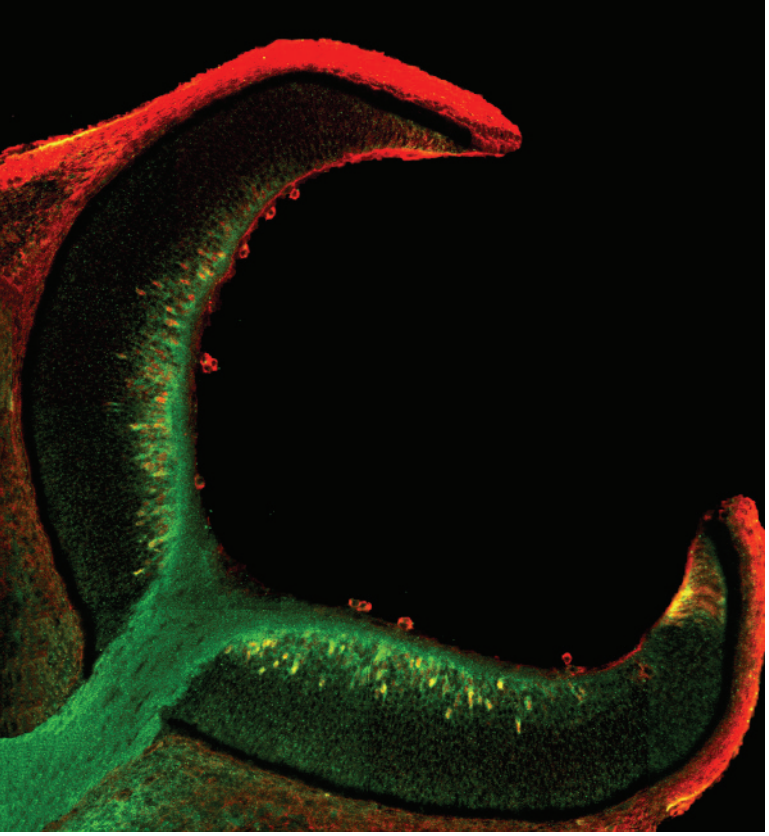
"In addition to the jumpy video stream, the visual system constantly receives feedback about the eye movements the brain is generating," says post-doctoral fellow **Ziad Hafed**.

To understand how the brain meets this challenge, the team asked whether human subjects perceived an object more clearly when they moved their eyes rather than staring at a fixed point. Subjects watched a video in which they glimpsed a partially hidden, circling chevron shape.

When subjects' eyes remained fixated, they perceived random lines moving up and down. But when they moved their eyes such that the input video streams remained unaltered, viewers easily recognized the lines as circling.

Krauzlis says that the human brain can readily fill in missing visual gaps. "When we see a deer partially hidden by tree trunks in a forest, we can still segment the visual scene, interpret the individual features, and group them together into objects," he says. "The striking thing is that moving your eyes can actually help resolve ambiguous visual inputs."

Ziad Hafed (left) and Richard Krauzlis



The proteins Vax2 (shown in green) and Pax6 (shown in red) cooperate to control the development of embryonic chick eyes. Pax6 regulates the development of the retina, while Vax2 ensures that the optic nerve is built.

Vax and Pax take turns to build an eye

Teams of proteins building the eye don't usually fraternize. One team creates the retina, while another constructs the optic nerve. But a recent study published by Salk scientists in *Genes and Development* shows that the two team foremen – the proteins Vax2, heading the optic nerve crew, and Pax6, head of the retina team – occasionally supervise the same work site.

In earlier studies, **Greg Lemke**, professor in Salk's Molecular Neurobiology Laboratory, had shown that building a proper eye required Vax2 to antagonize Pax6. But his lab had some intriguing data suggesting that Vax2 and Pax6 were co-expressed in the same cell at certain developmental stages.

Vax2 and Pax6 are transcription factors that normally function in a cell's nucleus by switching genes on and off. **Jin Woo Kim**, a former postdoctoral fellow in Lemke's lab, showed that although both proteins at times reside in the same cell, Vax2 shuttles in and out of the nucleus in response to extracellular signals, meaning that when Pax6 took over to construct the retina, Vax2 was effectively – but temporarily – cooling its heels in the cytoplasm.

That shuttling was controlled by a chemical modification known as phosphorylation. Kim engineered a Vax2 protein that could not be phosphorylated and then forced that protein into chick retinal precursor cells. The resulting chicks had no eye.

"What you had was a chicken with just a big optic nerve," says Lemke. "This basically says that you have to get this protein out of the nucleus. If you keep it there, you get no retina at all."

Most likely, mother nature doesn't simply dispose of Vax2 when she's finished with it because Vax2 is recycled for use later in development, Lemke says.

Targeted tumor therapy: When antagonists do a better job

Targeted radiotherapy lobs toxic payloads into tumor cells, leaving normal cells relatively unharmed. These missiles consist of radioactive bullets guided by small molecules – known as agonists – that recognize and bind to the limited number of activated receptors expressed on the tumor cell surface.

But Salk researchers, along with their collaborators in Switzerland, show in a study published in *Proceedings of the National Academy of Sciences* that it may be more efficient to exploit antagonists that bind to all receptors.

"Our findings mark a paradigm shift," explains **Jean Rivier**, professor in Salk's Clayton Foundation Laboratories for Peptide Biology. "Radiolabeled antagonists were never considered for targeted cancer therapy since they don't trigger internalization of the receptor/ligand complex." By contrast, agonists armed with radionuclides are internalized and destroy cells from within.

Peptide hormone-producing tumors expressing receptors for the hormone somatostatin are routinely targeted with radiolabeled somatostatin agonists for both diagnosis and treatment. These agonists have been used to treat neuroendocrine tumors, although improved tumor uptake and reduced toxicity are still desirable.

"Antagonists have properties that may improve the sensitivity of diagnostic procedures and improve the efficacy of radiotherapy," explains Rivier.

So his lab synthesized several synthetic somatostatin receptor antagonists. Then Swiss colleague Jean Claude Reubi of the University of Berne selected those that were most effective and Helmut R. Mäcke at the University Hospital in Basel evaluated how well they worked in vivo. When aimed at tumors in mice, these missiles were indeed effective.

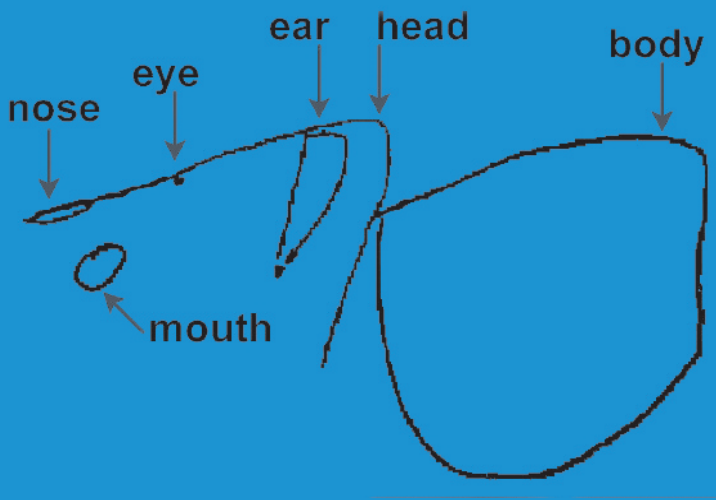
"The uptake of the antagonist-driven radioligands was particularly high in these tumors," says Rivier, adding, "A 60 percent uptake of all administered radioactivity has never been achieved before by any somatostatin receptor agonist, not even the newest ones."

Moreover, radioactivity persisted in tumors for a longer time than agonists resulting in lesser toxicity to organs like the kidney. Why would antagonists, which hang onto the outside of cells, be more effective weapons than agonists?

Rivier explains that agonists, in order to be internalized, likely bind to a select and limited set of conformationally favored receptors, making them less efficient than promiscuous antagonists that may bind to several different receptor conformations.

Jean Rivier

WILLIAMS SYNDROME, THE BRAIN, AND MUSIC



Children with Williams syndrome, a rare genetic disorder, just love music and will spend hours listening to or making music. Despite averaging an IQ score of 60, many possess a great memory for songs, an uncanny sense of rhythm, and the kind of auditory acuity that can discern differences between different vacuum cleaner brands.

A study by a multi-institutional collaboration of scientists, published in *NeuroImage*, identified structural abnormalities in a certain brain area of people afflicted with Williams syndrome. This might explain their heightened interest in music and, in some cases, savant-like musical skill.

Professor **Ursula Bellugi**, director of the Laboratory for Cognitive Neuroscience at the Salk Institute – the central hub of this unique scientific alliance– explains, "Understanding the connections between missing genes, the resulting changes in brain structure and function, and ultimately behavior, may help us to reveal how the brain works."

The current study is just the latest chapter in a story that's been unfolding for quite some time – gaining increasing momentum in recent years. It started when Bellugi reached out across disciplines and assembled a team of experts under the umbrella of a Program Project from the National Institutes of Child Health and Human Development to help her trace the influence of individual genes on the development and functioning of the brain.

Professor Allan L. Reiss, director of the Center for Interdisciplinary Brain Sciences Research at Stanford University and senior author of the current study, focuses on the overall morphology of the brain, while co-author Albert Galaburda, professor at the Harvard Medical School's department of Neurology, zooms in on the cellular architecture of the brain. Molecular geneticist Julie R. Korenberg, professor in the department of Pediatrics at UCLA, digs even deeper and studies the genes missing in people with Williams syndrome, whereas Debra Mills, associate professor in the department of Psychology at Emory University, concentrates on the neurophysiology, the electrical activity of behaving neural networks. Says Bellugi, who studies the cognitive aspects of the disorder: "Things are really starting to come together now."

Patients with Williams syndrome have an affinity for music and heightened social skills despite their below average IQ scores.

Identified more than 40 years ago, Williams syndrome arises from a faulty recombination event during the development of sperm or egg cells. As a result, almost invariably the same set of about 20 genes is deleted from one copy of chromosome seven, catapulting the carrier of the deletion into a world where people make much more sense than objects do.

"Williams syndrome is a perfect example where a genetic predisposition interacts with the environment to sculpt the brain in unique ways," says Reiss. "It provides a unique

window of understanding on how the brain develops under typical and atypical conditions," he adds.

People with Williams syndrome are irresistibly drawn to strangers, remember names and faces with ease, show strong empathy and have fluent and exceptionally expressive language. Yet, they are confounded by the visual world around them: While they can't scribble more than a few rudimentary lines to illustrate an elephant, they can verbally describe one in almost poetic detail.

"The discrepancy between their engaging social use of language and their poor visual-spatial skills is startling," says Bellugi. "I am confident that once all the evidence is in, we will have identified genes and pathways in the Williams syndrome deletion that underlie these drastic differences in modalities," she adds.

Despite whole brain volumes that are about 15 percent smaller than normal, the temporal lobe, which lies above the ear canal and, among other things, is involved in processing sounds and interpreting music and language, is of approximately normal size in people with Williams syndrome. In their study, the researchers tried to answer the question of whether an atypical development of the planum temporale, which is part of the temporal lobe and thought to be involved in many auditory tasks, including perfect pitch, may underlie the unusual musical and language skills.

First author Mark Eckert, assistant professor at the Medical University of South Carolina, and colleagues used data from brain scans of 42 individuals with Williams syndrome and 40 control participants to compare the surface folds of the planum temporale. In most people, the structure is larger on the left side of the brain than on the right. In people with Williams syndrome, however, the sides were symmetrical.

"There are different possible explanations. Either the left side didn't grow enough or the right side grew larger than usual," says Galaburda.

The folding pattern, in particular one groove called the Sylvian fissure, pointed to an increase size of the right planum temporale.

But size alone might not explain the unusual auditory strengths of people with Williams syndrome. A more general explanation includes variations in the connectivity of certain brain regions that might contribute to the specific strengths and weaknesses in Williams syndrome.

In recent studies, Galaburda had found that cells in the primary visual cortex of carriers of the Williams deletion are smaller and more densely packed – allowing for fewer connections between cells. Neurons in the primary auditory cortex, on the other hand, were larger and loosely packed, denoting increased "connectedness."

"These differences in cell size and density may underlie the strengths in auditory phonology, language and possibly music, and the difficulties in visual spatial construction for primary visual areas," says Bellugi. "This is really just part of the overall effect of the gene deletion on brain development."

"Relatively subtle developmental defects can have a significant impact on neurological function," says **Dennis O'Leary**, professor in the Molecular Neurobiology Laboratory at the Salk Institute, who studies the development of the cortex and sensory systems.

"This exciting work opens the door to develop explanations of how gene networks operating in the developing and mature brain to determine who we are and how effectively we behave and perform."

A young girl smiles for the cameras (top), another participates in a face-painting activity (middle), while a third sings during music hour at a holiday party hosted for Williams syndrome children by the Laboratory for Cognitive Neuroscience at Salk.

Image courtesy of Ursula Bellugi

"While they can't scribble more than a few rudimentary lines to illustrate an elephant, they can verbally describe one in almost poetic detail."

Scientist wins 2007 McKnight Neuroscience of Brain Disorders Award

Andrew Dillin, assistant professor in the Molecular and Cellular Biology Laboratory, has been selected for the 2007 McKnight Neuroscience of Brain Disorders Award. He will receive $300,000 over a three-year period to study "age-associated neuroprotection by insulin/IGF-1 signaling."

Established in 1986 by the McKnight Endowment Fund for Neuroscience, the Neuroscience of Brain Disorders Awards support innovative efforts aimed at translating basic laboratory discoveries in neuroscience into clinical benefits for patients. The awards are highly competitive: Only six out of 196 applicants were selected this year.

Like most neurodegenerative diseases, Alzheimer's disease usually appears late in life. Dillin's hypothesis is that the aging body continually produces proteins prone to aggregation, eventually leading to diseases such as Alzheimer's. To understand the consequences of age-onset protein aggregation and disease, Dillin has taken a multi-pronged approach and established key collaborations with Salk researchers **Roland Riek**, **Steve Heinemann**, and post-doctoral fellow **Ehud Cohen** and is continuing his strong collaboration with Scripps scientist Jeffery W. Kelly.

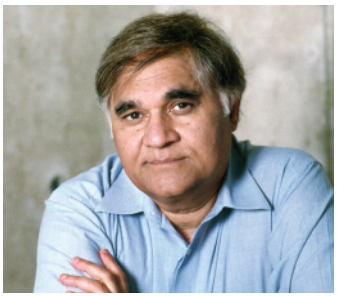
Andrew Dillin

He and his collaborators will examine how the worm *Caenorhabditis elegans* protects itself against toxic protein aggregation with age and will seek to evaluate whether the same protective mechanisms exist in mammals.

Dillin will also determine whether the same genetic pathways that regulate aging function to regulate protection against proteotoxicity. Ultimately, he will seek to identify the agent or agents implicated in age-related neurodegeneration. If successful, the work will generate preliminary data for an ongoing collaboration to probe the link between aging and the progressive degeneration of brain cells.

Born and raised in Reno, Nevada, Dillin earned his bachelor's degree in biochemistry from the University of Nevada in Reno and his doctorate in Molecular and Cellular Biology from the University of California at Berkeley. After completing a postdoctoral research fellowship at the University of California in San Francisco, he was recruited to the Salk Institute.

Terrence J. Sejnowski



Inder Verma

Professors Sejnowski and Verma named 2006 AAAS Fellows

Professors **Terrence J. Sejnowski** and **Inder Verma** have been awarded the distinction of AAAS Fellow. Election as a Fellow of the American Association for the Advancement of Science is an honor bestowed upon members by their peers.

Sejnowski, who heads the Crick-Jacobs Center for Computational and Theoretical Biology at the Salk Institute and an Investigator with the Howard Hughes Medical Institute, has been selected for his "outstanding contributions in computational neuroscience and for founding *Neural Computation*."

Sejnowski tries to understand the computational resources of brains and to build linking principles from brain to behavior using computational models. He pursues his goal by combining both experimental and modeling techniques to study the biophysical properties of the connections between brain cells and the population dynamics of large networks of neurons.

He recently showed that the release of chemical signals from nerves isn't restricted to synapses, the ends of nerve fibers in ciliary ganglia, as neuroscientists had previously believed, but is mostly released outside the expected region. *Neural Computation*, which he founded in 1989 shortly after arriving at the Salk Institute, is the leading journal in neural information processing in artificial and biological systems.

Verma, professor in the Laboratory of Genetics and American Cancer Society Professor for Molecular Biology, has been selected for his "pioneering use of lentiviral vectors to introduce foreign genes efficiently into brain, liver, muscle, retina, hematopoietic, and embryonic stem cells."

Verma joined the Salk in 1974 and quickly became one of the world's leading authorities on the development of viruses for gene therapy vectors. He and his colleagues established the use of stripped down versions of viruses, HIV in particular, that can deliver genes to non-dividing cells, which constitute the majority of cells in our bodies.

He has used these vectors to successfully deliver the clotting factor gene in laboratory animals to reduce the amount of an enzyme that is crucial to Alzheimer's disease development, and to transfer a therapeutic gene to retinal cells to mice with an inborn deficiency.

Paul Slesinger receives award for research on schizophrenia

Paul Slesinger

Paul Slesinger, associate professor in the Peptide Biology Laboratory, has been awarded the Independent Investigator Award by The Mental Health Research Association (formerly known as the National Alliance for Research on Schizophrenia and Depression, or NARSAD), the largest non-government, donor-supported organization that distributes funds for brain disorder research. The award, $100,000 over two years, will support Slesinger's research on mental disorders, such as schizophrenia.

Dopamine is a chemical messenger or neurotransmitter released by brain cells to relay information to other brain cells via receptors. A defect in the brain's dopamine system is implicated in schizophrenia, but the molecular nature of this defect remains unclear.

Dopamine receptors belong to a family of neurotransmitter receptors that interact with downstream proteins such as potassium channels. Potassium channels can alter dopamine regulation by changing neuronal membrane excitability. Recently, Slesinger discovered a novel type of potassium channel regulator called sorting nexin 27 (SNX27).

Interestingly, this SNX27 protein has been implicated in some types of drug addictions. With the award, Slesinger will examine whether potassium channel signaling in the brain is affected by SNX27. This type of regulation could represent a novel pathway for regulating electrical activity in neurons, and lead to the discovery of new drug targets for controlling dopamine activity in the brain.

Postdocs receive NIH Pathway to Independence Award

You-Wei Zhang (top) and Xiangmin Xu

Two postdoctoral researchers at the Salk Institute have each been awarded five-year grants as part of the National Institutes of Health's (NIH) new Pathway to Independence Program.

You-Wei Zhang and **Xiangmin Xu** are among 58 other recipients from around the country who have received the award designed to foster the young careers of today's most promising scientists.

"New investigators provide energy, enthusiasm, and ideas that propel the scientific enterprise towards greater discovery and push forward the frontiers of medical research," said Elias A. Zerhouni, M.D., director of the NIH. "We must invest in the future of our new scientists today if we expect to meet the nation's health challenges of tomorrow."

Working under **Edward Callaway**, professor in the Salk's System's Neurobiology Laboratory, Xu's studies focus on understanding how inhibitory neurons in the brain's cerebral cortex regulate brain activity. These studies have important implications for human health, as inhibitory neurons and their activities are involved in the cortical mechanisms that regulate attention and their disruption is implicated in schizophrenia.

Zhang's research, conducted under **Tony Hunter**, professor in the Salk's Molecular and Cell Biology Laboratory, focuses on dissecting the response of cancer to chemotherapeutic drugs, like irinotecan, that cause DNA damage. The goal is to understand how cancers can become resistant to chemotherapy so that new cancer therapies can be developed.

The Pathway to Independence Program is split into two phases: During the first two years, or mentoring phase, investigators complete their supervised research work, publish results, and search for an independent research position. The last three years, or independent phase, allow awardees who secure an assistant professorship to establish their own research program and apply for an NIH Investigator-Initiated (R01) grant. The R01 is the major means by which NIH supports individual scientists in the field.

Pathway to Independence awardees pursue new research directions and opportunities in a range of scientific areas, from basic research on cell biology and development of the nervous system to research focused on Alzheimer's disease, cardiovascular disease and HIV/AIDS.

"In today's challenging budget environment, it is critical that NIH preserve the ability of young scientists with fresh ideas to enter the competitive world of NIH funding," said Zerhouni.

National Academy of Sciences honors Joe Ecker with Carty Award

The National Academy of Sciences has selected **Joseph R. Ecker**, professor in the Plant Biology Laboratory and director of the Salk Institute Genomic Analysis Laboratory, to receive the 2007 John J. Carty Award for the Advancement of Science "for contributions in the areas of ethylene signal transduction and Arabidopsis genomics that have paved the way for a revolution in modern agriculture."

Given annually for noteworthy and distinguished accomplishments in science, it was established by the American Telephone & Telegraph Co. in honor of John J. Carty and has been awarded since 1932. The honor includes a medal and a $25,000 prize that will be presented in Washington D.C. at the organization's annual meeting April 29.

Ecker is internationally recognized for his pioneering contributions to plant genomics. Early on, he advocated the mapping and sequencing of the genome of the tiny mustard weed *Arabidopsis thaliana* and directed much of the sequencing project.

Commonly known as thale cress, *Arabidopsis* was the first flowering plant to have its entire genome unlocked. *Arabidopsis* is now widely considered one of the most important model organisms for the study of plant genetics and genomes thanks in large part to the genome project.

In addition, Ecker's groundbreaking research on the gaseous plant hormone ethylene has yielded fundamental insights into the mechanisms of plant growth control and has led to the development of technologies that delay fruit ripening and disease processes.

Joseph Ecker

Tatyana Sharpee

New assistant professor joins Laboratory of Computational Biology

Tatyana Sharpee has joined the Salk's Laboratory for Computational Biology as its newest assistant professor. She comes to the Institute from the Sloan-Swartz Center for Theoretical Neurobiology at the University of California in San Francisco.

Born and raised in Russia, Sharpee received her master's degree in theoretical physics from the Ukraine National University in Kiev. During her thesis research at Michigan State University, she studied such quantum phenomena as tunneling of electrons in a magnetic field before she turned her attention to brain cells.

The perennial quest of neurobiologists centers on the question how the brain codes and processes information. In the past, scientists had to rely on simplified objects on a computer screen to garner information on how the brain processes visual information and makes sense of its environment, for example.

Sharpee developed a statistical method that allows her to analyze the response of brain cells to natural stimuli such as a short video clip shot during a stroll on a forest trail. Using this approach, she discovered that brain cells adjust their filtering properties to most efficiently process the incoming information.

"Humans are remarkably good at multiple tasks that cannot be performed by machines, yet biology demonstrates that it is possible," says Sharpee. "Once we understand how it works, it will have important implications for everyday life."

At the Salk, she will continue to study optimal coding and plans to expand her method to include higher level brain cells, which are very specific to particular combinations of stimulus features – such as a person's face or individual songs of songbirds. These cells are also surprisingly flexible and recognize a face whether it is very close or far away.

New grant program funds Institute's most promising, cutting-edge research

Innovative research in the beginning stages offers the most promising breakthroughs. At the Salk Institute, such work brings together some of the world's most creative minds to explore uncharted scientific territory.

But innovative science also brings challenges, particularly in how it's funded. Most government grants fund research with more predictable results – forcing scientists working on cutting-edge research to look elsewhere for support.

That's why the Institute has established the Innovation Grants Program. It is designed to provide philanthropists the opportunity to make a significant impact by donating seed funding for the Salk's new and emerging research.

It marks the first time a grant program has been specifically created for the most cutting-edge studies and awarded through a competitive selection process.

To date, two gifts have been received to help launch the new Innovation Grants Program – nearly $400,000 by Joan and Salk Board of Trustees Chairman Irwin Jacobs; and more than $500,000 by the late philanthropist Elizabeth Rodriguez to establish The Elizabeth O. Rodriguez Endowed Fund for Innovative Grants.

As a result, four, one-year grants ranging between $25,000 and $100,000 have been awarded to Salk researchers. They include: **Gerard Manning**, senior staff scientist in the Razavi-Newman Center for Bioinfomatics; **Joanne Chory**, professor and director of the Plant Molecular and Cellular Biology Laboratory, together with **Joseph Noel**, professor in the Jack H. Skirball Center for Chemical Biology and Proteomics; **Edward Callaway**, professor in the Systems Neurobiology Laboratory; and **Samuel Pfaff**, professor in the Gene Expression Laboratory.

The Callaway lab, for example, received an $80,000 award to support development of a novel method designed to allow a detailed understanding of how individual neurons integrate information from the thousands of synaptic connections they receive from other neurons.

The method would allow all of the neurons that converge onto a single cell to be independently stimulated by precisely timed light pulses so that specific spatial and temporal input patterns could be generated.

Philanthropists will have the opportunity to hear about these studies and proposals for other promising areas of research beginning in the spring when interested donors will be invited for a special breakfast at the Salk Institute. Friends and donors of the new Innovation Grants Program will also receive periodic written updates on the research they have selected.

To receive an invitation to the 2007 Innovation Grants Program breakfast event and/or to learn more about ways to support the Innovation Grants Program, please contact Kristin Bertell at bertell@salk.edu or 858-558-8552.

New York luncheon builds bridges and keeps contributors involved

The Salk Institute will host two Taste of Discovery luncheons for specially invited donors and friends April 26 and again in the fall. The semi-annual events provide a unique opportunity for friends of the Institute to hear about the latest groundbreaking research underway in the laboratories in an intimate setting.

More than 100 guests attended the October 2006 luncheon at the Harmonie Club where **Joseph Noel**, professor in the Salk's Jack H. Skirball Center for Chemical Biology and Proteomics, discussed how chemicals found in everyday foods can cure and reverse human diseases. Morgan Stanley underwrote the event.

Inder Verma, professor in the Laboratory of Genetics and chair of the Salk's Academic Council, is the scheduled speaker for the April 26 luncheon. A member of the National Academy of Sciences who has received numerous scientific awards for his contributions to cancer research, Verma will give a presentation titled "Cancer – A Malady of Genes."

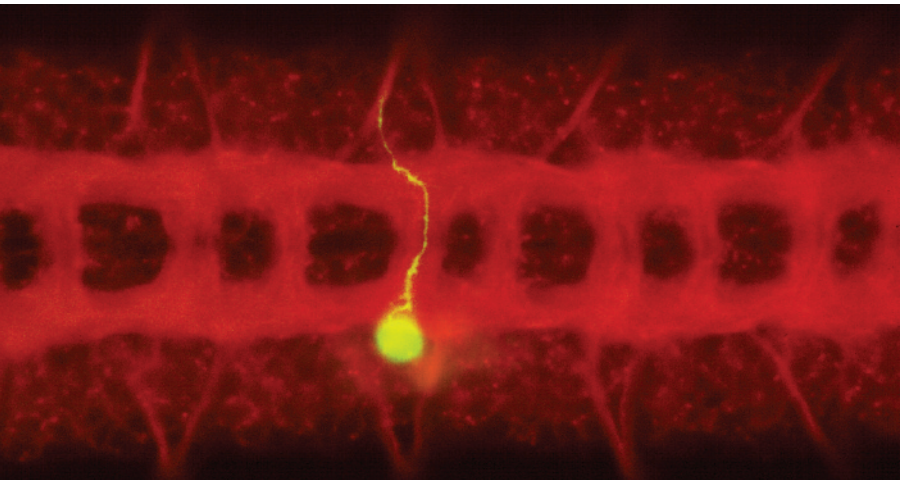
Salk President Richard Murphy will also provide an update on Institute activities and introduce the newly appointed Chairman of the Board of Trustees Irwin Jacobs, co-founder and chairman of the Board of Qualcomm Inc. Qualcomm is the world leader of Code Division Multiple Access (CDMA) digital wireless technology. Jacobs has led the commercialization of CDMA technology and its success as the world's fastest growing voice and wireless communications technology.

"The Salk Institute is an international institution with many of our Board of Trustees, International Council members, donors and friends located on the East Coast and abroad," says Dianne Day, vice president of Development at the Salk. "Many of our events, such as the luncheons in New York, help build bridges between Salk and our constituency around the world by keeping them involved and informed, while also introducing the Institute to new friends."

Renate and Adolf Hassen (from left), Inge Stephens and Joe George were among more than 100 guests at the New York Taste of Discovery luncheon last fall.

INSIDE SALK

In 1960, just five years after developing the first safe, effective vaccine against polio, Jonas Salk, M.D., founded the institute that today bears his name. Home to 11 Nobel Laureates since its founding, the Salk Institute for Biological Studies is a world leader in basic research on the biological principles governing life at all levels, from the individual cell to an entire population. For more information: www.salk.edu.



Scientists study the embryonic nervous system of the fruit fly Drosophila to understand how neurons assemble during development to produce functioning nervous systems. The portion pictured here is the fly counterpart to the vertebrate spinal cord. A developing nerve cell (yellow) has been filled with a fluorescence dye. Its projecting axon will eventually find its target cell to make a synapse. Other nerve cells and their axon projections are labeled in red. Photo courtesy of John B. Thomas, professor in the Molecular Neurobiology Laboratory.

Calendar

JULY 13–17, 2007
Cell Cycle Symposium

AUGUST 8–12, 2007
Mechanisms and Models of Cancer Symposium

AUGUST 25, 2007
Symphony at Salk

For additional information about these and other Salk events, please contact Institute Relations at 858.453.4100 x1658.

Sign up for update

Richard Murphy, Ph.D., Salk Institute's president and CEO, regularly publishes a free electronic newsletter, called *Update for Salk Institute Friends*, that briefly describes recent research discoveries and upcoming public events. To sign up, email: update@salk.edu.

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