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THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

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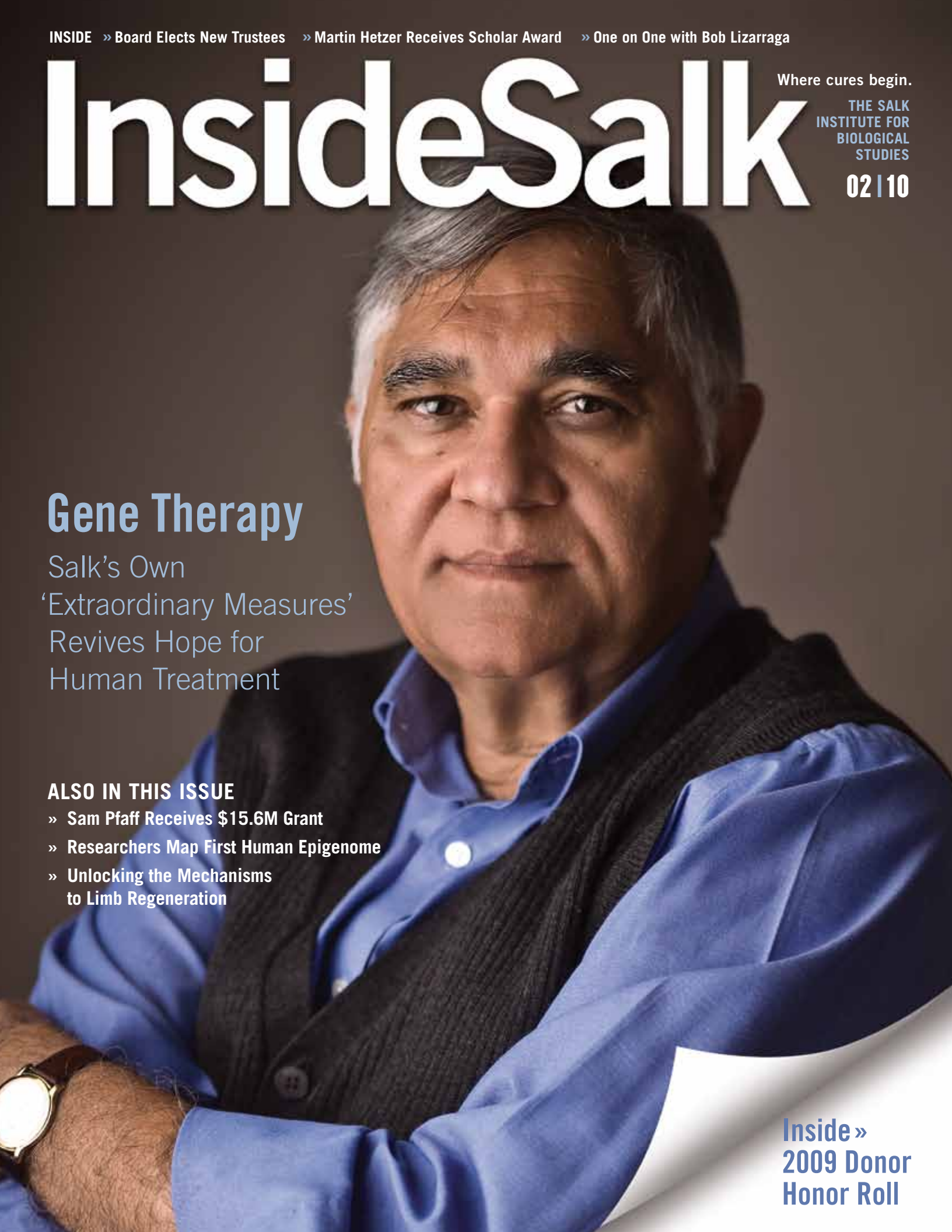

Gene Therapy

Salk's Own 'Extraordinary Measures' Revives Hope for Human Treatment

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February 2010
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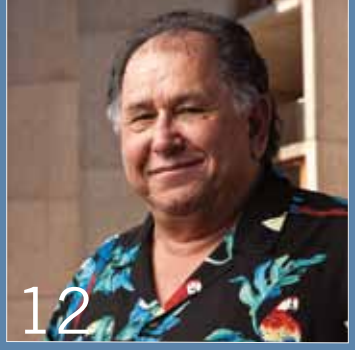
Three sisters help two terminally ill boys.



One on One with Bob Lizarraga

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ON THE COVER

Inder Verma's breakthrough of using a lentivirus for gene therapy was successfully used to treat two boys suffering from a terminal brain disease.

Investing for the Long Term

Dear Friends,

OUR SOCIETY HAS BECOME INCREASINGLY SHORT-TERM FOCUSED, perhaps most exemplified by quarterly earnings. But the solution to many of the biggest challenges facing our country – from the economy to the environment, to improving health – requires long-term thinking. The same principle can be applied to funding for basic research.

Our story of a recent success in gene therapy underscores the need to take a long-term view. Anyone who has followed the 20-year-old field of gene therapy knows that the road has been extremely rocky. Initially heralded as a means to cure many genetically based diseases, much like an overhyped stock offering, gene therapy fell sharply out of favor after some troubling clinical failures.

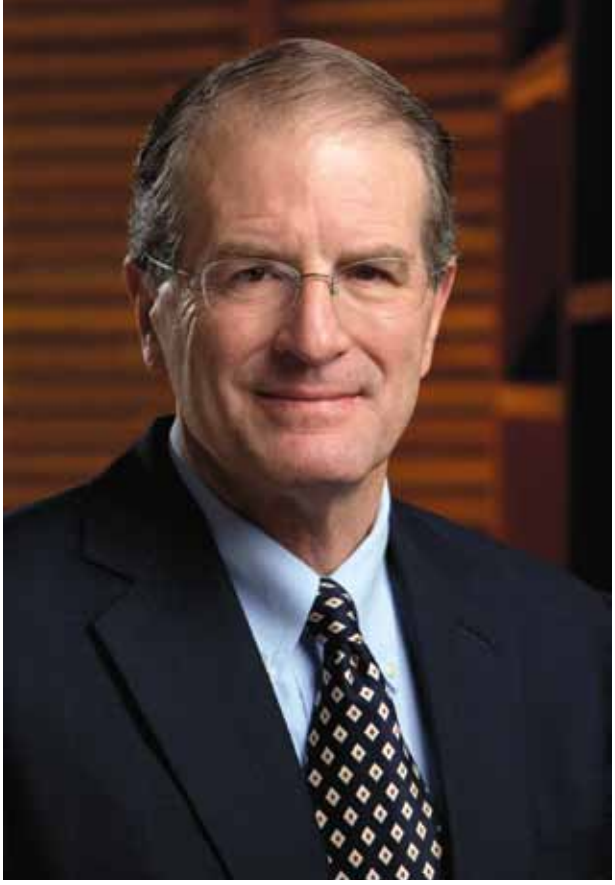
But as the *New York Times* reported on Nov. 5th 2009, successes in giving new genes to correct specific inherited diseases suggests the technology may have a bright future after all. A French research team used gene therapy based upon a tool developed at the Salk Institute to effectively treat adrenoleukodystrophy (ALD) in two Spanish children. The French scientists used a safe version of the deadly AIDS-causing virus to deliver healthy genes into two young boys – children who otherwise faced likely death before adolescence from the progressive brain disease.

Our own Professor Inder Verma first imagined this unexpected use of the fearsome AIDS virus back in 1993. After several years of experiments employing the Salk's highly creative and collaborative brand of science, he published seminal papers on his viral vector discovery. And 11 years after Verma's inspiration, the viral vector was used to treat two kids half a world away. Their deteriorating condition appears stabilized.

The history of Inder's scientific feat and its ramifications is the subject of our *Inside Salk* cover story. But it is the 2009 science policy context of that discovery that I am most eager to underscore. You see, a basic science breakthrough has a life cycle, and that cycle is typically far longer than one would expect. It took about 15 years from Inder's first Aha! moment to the report of encouraging treatment of these children. No one could have accurately predicted the precise, convoluted path from original idea to human use.

When Salk scientists publish their groundbreaking work, the implications can take years or even decades to become manifest. Thus, my take-away message is that basic science requires long-term investment and long-term perspective.

Unfortunately for the Salk Institute and other basic science bastions, federal funding for fundamental research is flattening. Increasingly, there is pressure on the National Institutes of Health (NIH) to funnel more dollars toward translational science in the belief it may provide more immediate application to patients. While this may be true in some cases, the history of breakthrough treatments of various diseases is that the road is generally long and full of many unanticipated detours.



William R. Brody

As a member of the Scientific Management Board of the NIH, it is my role to persuade our federal policymakers to once again more fully embrace the long-term view and not short-change basic research. I believe wholeheartedly that the knowledge base and discoveries developed through superb basic science are essential to the American innovation and leadership we have all come to expect. Limiting the opportunity for scientific ingenuity to flourish is not a smart strategy.

At the same time, under the most optimistic scenarios we cannot anticipate the same kind of growth in federal funding for biomedical research we experienced in the last decade. Hence, there is a growing and urgent need for private foundations and individual philanthropists to invest in basic research, particularly in the type labeled high-risk and potentially high-reward. Exceptionally valuable are unrestricted gifts and contributions to our endowment that give us the flexibility to invest in the bright ideas of the future Inder Vermas – those whose out-of-the-box schemes will ultimately lead to innovative and effective treatments for serious disease.

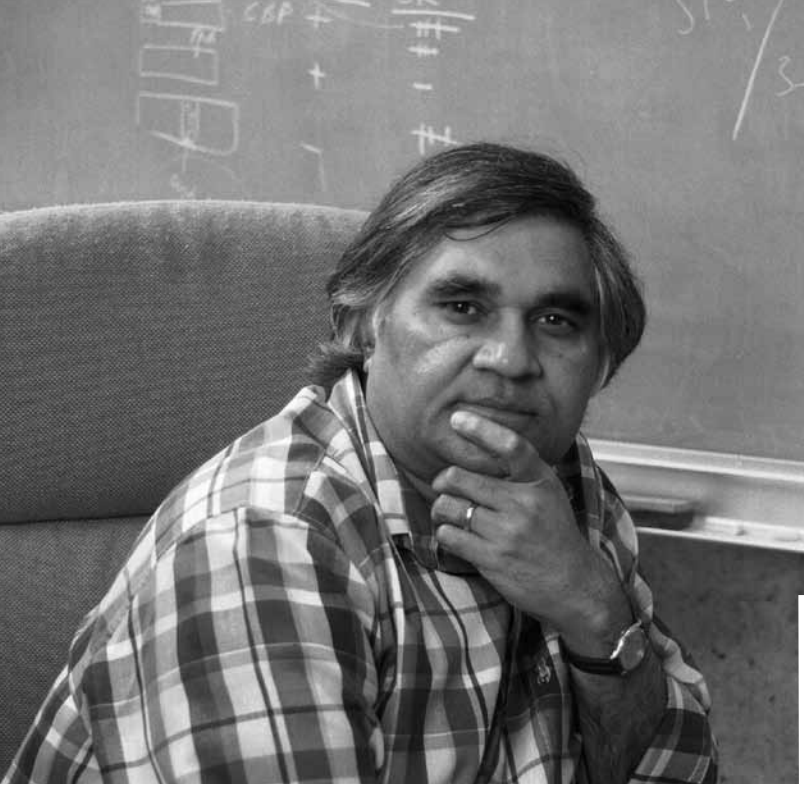
Thanks to our many private contributors who understand the long-term nature of basic research, the Salk continues to move science forward. Inder Verma's breakthrough in gene therapy is just one compelling example of how your support of the Salk Institute is, in the long run, a valuable and extremely wise investment in improving human health.

William R. Brody, M.D., Ph.D.
Irwin M. Jacobs Presidential Chair

Saving Lives

With striking parallels to the Hollywood film "Extraordinary Measures," one landmark discovery from Salk, a French research team and three determined sisters help two Spanish boys survive a fatal genetic disease.

Editor's Note:
In November of 2009 a French research team reported an amazing breakthrough. They had stopped the frightening progress of a fatal brain disease in two young boys in Spain by using a novel type of gene therapy. Not readily apparent in ensuing international headlines was the Salk Institute discovery that made this gene therapy possible. Here is the story behind the story.



Working with a UCSD scientist, Inder Verma successfully repaired a human genetic defect in animal cells in the 1980s.

IT WAS THE EARLY 1990S AND SALK PROFESSOR INDER VERMA had the deadly Human Immunodeficiency Virus (HIV) in his sights. One of his institute colleagues had contracted AIDS after receiving infected blood during heart bypass surgery, and Verma witnessed the terrible efficiency of the virus and the dreadful consequences of the disease.

The HIV was proving a fierce adversary to researchers the world over. During the previous few decades, biologists had developed a basic understanding of how viruses like HIV work. A virus inserts itself into or otherwise hijacks our cells, using our cellular machinery to rapidly reproduce. Most viruses prey on our dividing cells, happily multiplying until our healthy immune systems prevail. But one of the HIV's most fearsome aspects is that it can also introduce itself into the genes of our non-dividing cells, like the cells in our brains and the immune system.

Verma, the American Cancer Society professor of Molecular Biology in the Salk's Laboratory of Genetics, started thinking about this unusual characteristic of the HIV in a rather radical and unexpected way. What if, he thought, "we could engineer the virus, entirely removing its ability to cause disease, while retaining its ability to enter non-dividing cells?"

Verma was already deeply engaged in the emerging field of gene therapy, and had an impressive track record of achievement. About 10 years prior Verma and a UCSD scientist successfully repaired a human genetic defect in animal cells in a Petri dish, making front-page news in *The New York Times*. He knew that there were limits in the choice of viruses that could be used to therapeutically deliver healthy genes (known as viral vectors). The available vectors could only effectively deposit their cargo into (correct the genetic defect in) dividing cells.

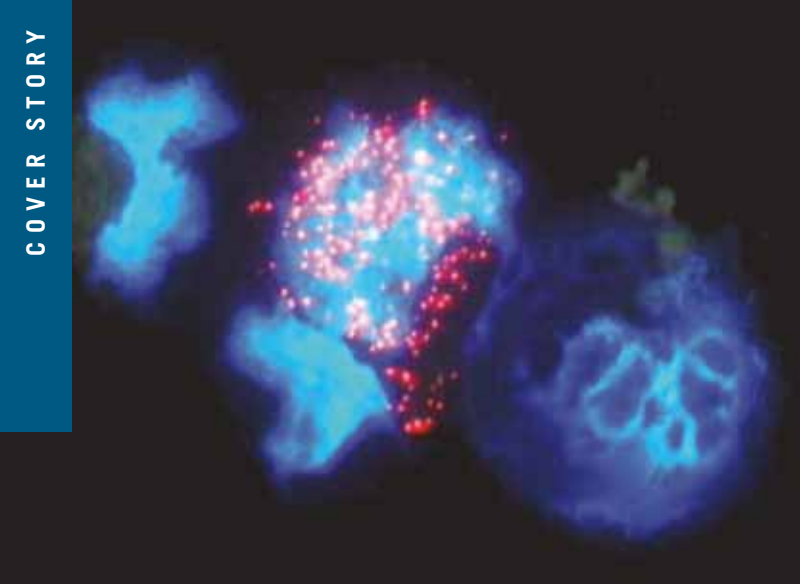
Here was this dangerous, yet intriguing HIV from the lentivirus family. Could Verma and his colleagues strip the HIV of its powers to cause AIDS, making it possible to use the defanged lentivirus to target areas like the nerve cells in the brain, or the rare population of stem cells that make our blood and the immune system?

Back row: Fred H. Gage, Didier Trono, and Inder Verma
Front row: Ulrike Bloomer and Luigi Naldini

The Stars Align

THE SALK INSTITUTE HAD JUST ESTABLISHED AN INFECTIOUS disease laboratory working on AIDS, and one of the first faculty to join this group was **Didier Trono**, who knew how to grow the AIDS virus in the laboratory setting. Verma had recently taken on a young Italian post-doc named **Luigi Naldini** who was inclined to pursue this potential gene therapy tool. Moreover, Professor **Rusty Gage** had recently joined the Salk faculty. Gage had valuable expertise regarding mice and their nervous systems, and was a generous collaborator. A young German MD, **Ulrike Bloomer** from Gage's laboratory, was assigned to collaborate with Naldini.

In a recent interview with *The New York Times*, Naldini, who is now director of the Institute for Gene Therapy at Vita-Salute San Raffaele University in Milan, Italy, recalled his days at the Salk working on the HIV as a potential viral vector. "We were scared of course," he admitted. But Naldini knew that if he could remove enough of the genetic material that causes AIDS, he could render the virus harmless while preserving its key transportation function.



The red areas show bone marrow cells that received a corrective gene in a Spanish patient who underwent gene therapy using the lentivirus to fight a terminal brain disorder.

Verma and his team developed a way to incapacitate the virus so completely that all it could do was convey the genes. Their April 12, 1996 paper published in *Science* offered this concluding sentence: "We believe that the generation of safe and efficacious lentiviral vectors will significantly advance the prospects of human gene therapy." The paper made quite a stir. It was the scientific version of "beating swords into plowshares," Verma said, chuckling at the memory.

"Next we had to show that the virus could carry a foreign gene and had the ability to introduce that gene into other non-dividing cells and tissues in mice," he said. The team performed its exacting work, yielding a second *Science* paper in 1997, demonstrating that they could actually use this new viral vector to deposit a gene into bone marrow in mice and that gene would now be appropriately expressed. "We made the vector completely safe and showed it could be used to treat genetic diseases," he said.

After years of creative and intensive work, the Salk team had made a seminal basic science contribution to the gene therapy field – conceiving a novel use for the deadly HIV and proving, in animal models, that it could be harnessed to convey healthy genes. It was time for others to carry the ball toward potential human use of this new vector.

Verma and the Salk Institute patented the discovery in 1996 and then licensed it to a Bay-area biotech start-up company called Somatix Therapeutics (Verma and Gage were both co-founders) which later merged with Cell Genesys. The company's role was to develop gene therapy tools like his lentiviral vector and it seemed a reasonable match.

Michael T. White, senior director of the Salk's Office of Technology Management and Development, says it was a genuine breakthrough to have devised a viable delivery system for ferrying healthy genes into non-dividing cells, and the company could have pursued its development. But the merged company wanted to concentrate on what its leaders perceived to be the best opportunities for maximum sales at that time. So Cell Genesys initially focused on gene therapy systems for cancer and "back-burnered the lenti system," White said.

Dark Days for Gene Therapy

MEANWHILE, TOWARD THE END OF THE DECADE, THE ENTIRE field of gene therapy was buffeted by some dramatic, high-visibility setbacks. Most notable was the death of 18-year-old Jesse Gelsinger, the first person to die in a gene therapy clinical trial. Gelsinger suffered from a form of genetic liver disease that can be fatal in infants. He joined a clinical trial at the University of Pennsylvania and was treated with healthy genetic material carried by an adenoviral vector (a DNA virus vector) in an experiment intended to demonstrate the safety of the procedure. He had a massive immune response to the viral vector, triggering multiple organ failure. Gelsinger died four days after the therapy, in September of 1999.

(Verma co-chaired the NIH-RAC Committee to investigate the circumstances and causes of this unfortunate development, testified at a U.S. Senate hearing and made recommendations to reduce the likelihood of recurrence of this tragedy.)

> "It was a genuine breakthrough to have devised a viable delivery system for ferrying health genes into non-dividing cells."
>
> – MICHAEL T. WHITE

Shortly after Gelsinger's death, in 2000 in France, a separate clinical gene therapy trial began to treat a form of SCID (Severe Combined Immunodeficiency), commonly known as Bubble Boy Syndrome. SCID is a genetic disorder that renders its victims extremely vulnerable to infections. Gene therapy improved the immune systems in 18 of 20 patients treated, and was labeled a success. But the trials were halted when it was discovered that the gene-carrying retroviral vector (a distant cousin of the lentiviral vector) was depositing its material in the wrong place in the human genome, inadvertently turning on an oncogene. Five of the children have so far developed leukemia; one died of it.

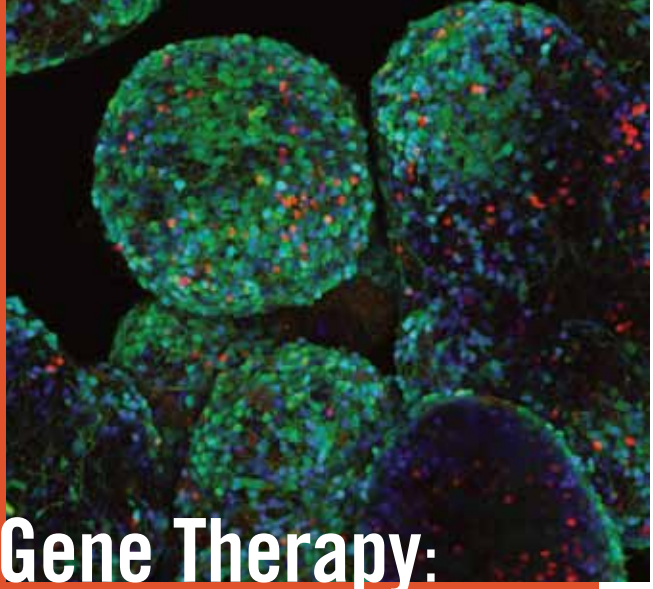
These setbacks were hardly surprising in the early days of gene therapy, White says. Furthermore, the journey from laboratory bench to human use for any drug or biological application is steeply uphill. Promising discoveries can languish as biotech start-up companies may only invest in developing one product at a time. Even when a discovery is fast-tracked, it can take anywhere from one to 10 years or longer to pass through all of the investigative stages and reach the FDA for licensure. Then more time passes while the government reviews it. Ultimately, for new drugs, for example, only one in 100 make it to the marketplace.

The highly publicized clinical tragedies choked initial optimism about gene therapy, increasing caution among scientists and clinicians, and slowing progress. In that less enthusiastic environment, "the problems associated with gene therapy took about 10 years to understand and resolve," White said.

While researchers on both sides of the Atlantic were studying the underlying issues brought to light by the clinical trials, a trio of American women was mobilizing for a personal life-and-death struggle. Amber and Rachel Salzman and their sister Eve Lapin committed to speed up research on behalf of children born with adrenoleukodystropy or ALD, a disease of the fatty insulation (myelin) surrounding nerve cells. ALD is an inherited disorder, invariably fatal in children about two to five years after diagnosis. (ALD was the subject of the 1993 Oscar-nominated film *Lorenzo's Oil* starring Nick Nolte and Susan Sarandon.)

In December of 2000 Lapin, of Houston, learned that her son Oliver had ALD and probably only a few years to live. After further testing, both Lapin's younger son and Amber's baby boy had the biochemical marker for ALD; both mothers were carriers. Rachel, a veterinarian by training, was not a carrier.

From left: Eva Salzman Lapin, Rachel Salzman, and Amber Salzman



Scientists targeted stem cells (pictured) for the recent study using a lentivirus. Image courtesy of Todd McFarlen, Salk Institute.

Gene Therapy: A Brief Primer

GENE THERAPY INVOLVES INSERTING HEALTHY genes into an individual's cells to treat a particular disease. In the 1980s, as scientists identified the underlying genetic abnormalities associated with many inherited diseases, gene therapy appeared to be an increasingly plausible approach.

The original focus of gene therapy was diseases caused by single-gene defects, such as cystic fibrosis, hemophilia, muscular dystrophy and sickle cell anemia. Today much broader applications are also envisioned, including treatments for cancers, neurological, cardio-vascular, and infectious diseases. In fact there are not many aspects of human health whose outcome cannot be influenced by gene therapy.

Gene therapy, though several decades old, is a technology still in its infancy. There are sobering biological challenges associated with the therapy: delivering the right genes to the right places without disrupting the genome or causing other disease; avoiding triggering the body's natural immune response to the new genetic material; and maintaining a lasting positive effect in cells.

The most common gene delivery method is via a virus. Viruses are extremely good at slipping into host cells and inserting genes into the host's genome. For this reason viruses seemed the obvious delivery tool. But viruses also can pose a variety of potential risks to human patients. In a few early clinical trials the viral vectors inserted themselves into the cellular genome next to a known cancer-causing gene and activated it, causing leukemia in some patients. And in 1999 one patient (18-year-old Jesse Gelsinger at the University of Pennsylvania) received a viral vector, triggering an immune response that killed him.

Despite these obstacles and setbacks, gene therapy has also shown considerable promise. Scientific breakthroughs continue to move the therapy toward medical application and to give patients and their families cautious hope for cures.

> "He was very helpful and supportive, I don't underestimate how much Inder's involvement helped us."
>
> – AMBER SALZMAN

Amber's son was only a year old, yet she understood the situation was urgent. "We knew we had only four or five years to find a cure," she said. Two months after receiving the dire news, Amber and Rachel met in Paris with scientists Patrick Aubourg and Nathalie Cartier of Inserm, a French research institute, to learn about the latest work on ALD and gene therapy in lab animals. And within three months of Oliver Lapin's terrible diagnosis, the three sisters formed the Stop ALD Foundation, supporting scientific collaboration leading to effective treatments and a cure for ALD.

At that time Amber Salzman was a senior executive at GlaxoSmith-Kline. She and Rachel started consulting experts within and outside her company, and "read through every journal." It was Amber's GSK boss, Tachi Yamada, who urged her to explore the use of gene therapy. And in 2001 they began meeting with scientists to do just that.

As she learned more about it, Amber Salzman recognized that a gene therapy solution could not come soon enough to help her son or nephews. Indeed, Oliver died in 2004 at age 12. His younger brother, Elliott, and her son, Spencer Barsh, were candidates for traditional bone marrow stem-cell transplants, the only existing treatment option, but no marrow matches were available. In 2002 the two young cousins received stem cell transplants from umbilical cord blood. (Use of cord blood, which contains early, undifferentiated cells, mitigates the body's immune response to foreign marrow.)

However, such transplants carry their own set of serious risks, most particularly the enduring possibility of an immune system reaction to foreign transplanted cells. Spencer, now 9, "almost died three times and it was a brutal procedure" involving three months in the hospital, Amber says. Today he is healthy and suffers no lasting ill effects. But his older cousin Elliott, now 15, suffers from graft-vs.-host disease and uses a wheelchair.

Having gone through the harrowing traditional transplant process "we felt very strongly that we needed to do something differently," Amber Salzman said. And that something was gene therapy.

A Match Made in Heaven

AROUND THE TIME AMBER AND RACHEL SALZMAN STARTED exploring gene therapy options, Inder Verma was elected the fourth president of the American Society of Gene Therapy (ASGT), thereby becoming a leading spokesman. The sisters were desperate to find a way to address ALD. And Verma had personally developed a viral vector with the ability to enter brain cells – the very types of cells affected by ALD. A meeting was essential.

"The first time I met him, I thought, 'Oh God, I'm talking to this brilliant scientist,' " Amber Salzman said of Verma. "But he puts you at ease. He likes people, likes helping…here was a top-notch scientist with a humanitarian side."

Verma recalled their first meeting, at an ASGT conference in Seattle in 2001. He learned that the French scientists were experimenting with retroviruses to treat ALD in mice. "But that was not very efficient," he said. "I wanted them to use the lentivirus." Amber told him they needed his help.

At their next meeting, shortly after the 9-11 tragedy, convened at the Hilton at a London airport, Aubourg and Cartier were also in attendance. "They showed me the data," he said. "I could see they needed a better and more efficient vector." Convinced the French group needed his lentiviral vector, Verma went back to Cell Genesys and helped persuade the company to make the vector of the quality required for human treatment. (Ultimately Cell Genesys licensed Verma's lentivirus technology to San Diego's Invitrogen to be marketed to other researchers as lab experiment kits; these kits have been widely used. And in March of 2008, Cell Genesys sold the technology to another company.)

Back in 2001, the lentiviral vector had never been used in people. It was expensive to prepare. And Verma was asking Cell Genesys to do all this to treat a rather rare disease. "But it appeared that it was well worth the trial," he said.

Over the past eight years the Salzmans have pushed and prodded to move the science, the scientists and the relevant companies forward. "We were pretty annoying," says Amber now, sounding only slightly rueful. The sisters strongly believed it was their role to make sure the scientists continued to talk to each other, "connecting the people and the pieces." "To Inder's credit, when I called him, he'd call me back within 24 hours," Amber said. "He was so engaged, and so patient at both a scientific and personal level. I feel like he's a member of my family.

"While he was very helpful and supportive," she continued, "he was always concerned about the scientific rigor of the work." Verma demanded, for example, that Aubourg publish his animal data for peer review. "I don't underestimate how much Inder's involvement helped us," she said of Verma.

» WEB EXTRA

Comments by Amber Salzman of The Stop ALD Foundation on Gene Therapy Success for ALD
www.salk.edu/insidesalk/genetherapy2

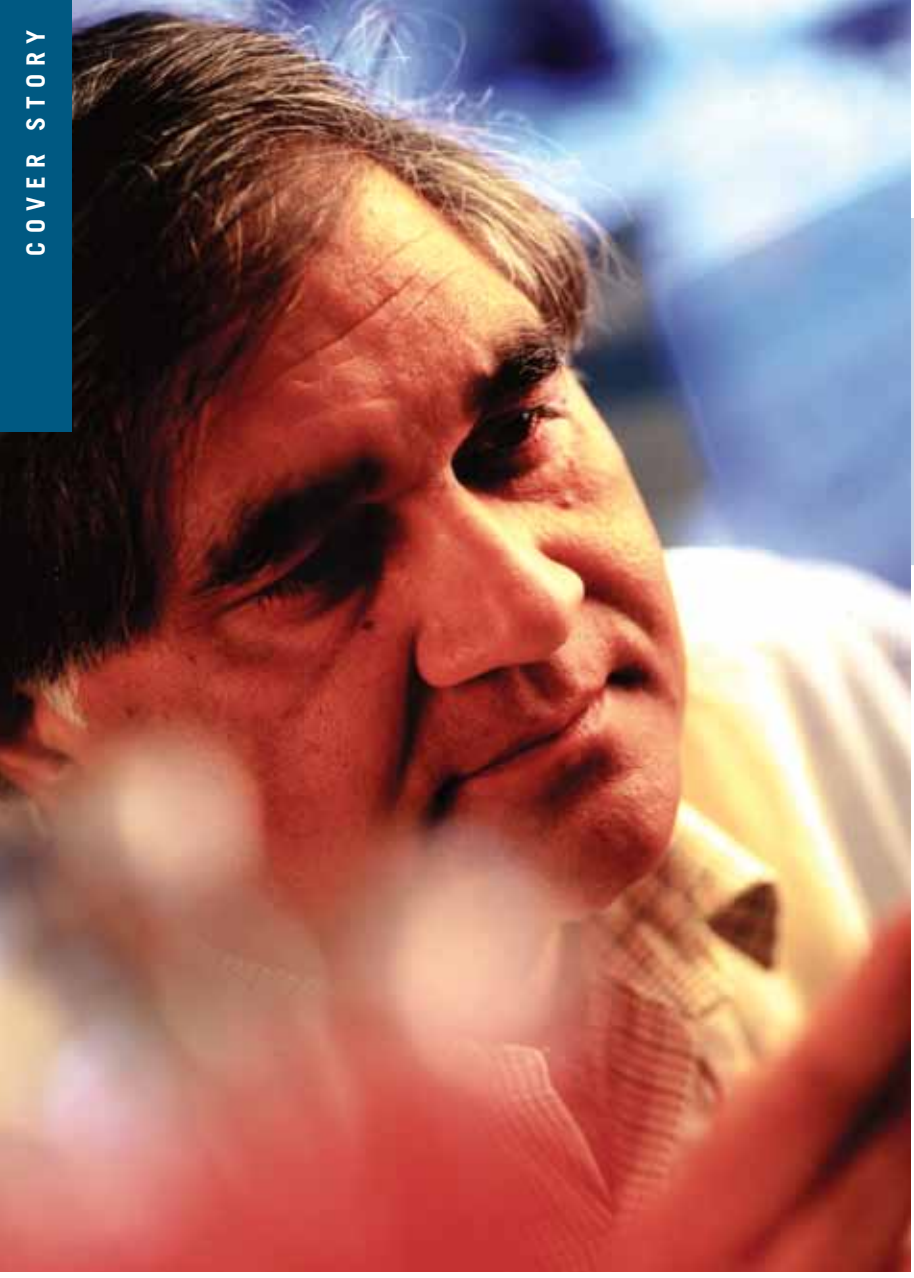


Photo of Inder Verma by Bill Santos (1999).

The Comeback Kids

IT TOOK SEVERAL YEARS FOR THE FRENCH SCIENTISTS TO PERFORM THE NECESSARY PRECLINICAL WORK with animals and for Cell Genesys to prepare a lentiviral vector suitable for use in a human clinical trial. Finally, in 2006 and 2007, two 7-year-old boys in Spain, both ALD patients with brain lesions characteristic of the disease, received the gene therapy treatment. It was the first time the lentiviral vector was used in humans who did not already have HIV infection.

The beauty of adding gene therapy is that it allowed each boy to be his own stem cell donor, correcting his own cells and eliminating the need to find matching bone marrow with the potentially lethal effects of foreign cells. The treatment began with the removal of some of each patient's bone marrow stem cells. Then the lentiviral vector was used to deliver healthy genes into the cells in a laboratory procedure. The treated marrow cells were then injected back into the patients, so each received his own improved cells.

In a Nov. 6, 2009 paper in *Science*, Aubourg and Cartier published their initial very promising results, triggering a media barrage. "Gene therapy makes major stride in Lorenzo's Oil disease," declared the *Los Angeles Times* that same day. "Gene therapy turnaround," said *The Scientist* on its newsblog. "For Gene Therapy, Seeing Signs of a Resurgence," *The New York Times* reported. "Gene Therapy for Fatal Brain Disorder 'Just the Beginning'," suggested *U.S. News* and *World Report*.

Amber Salzman, who is now the CEO of Cardiokine Inc., a biotech company developing heart medicines, expressed considerable satisfaction with the early results of the gene therapy trial. The young Spanish boys needed only about a month in the hospital and experienced a far gentler procedure than her own son, she said. The gene therapy has arrested the disease

> "The work done by Dr. Verma and his team at the Salk was really pioneering, representing a quantum leap forward." – DONALD B. KOHN

and both boys in Spain are leading normal lives. (A third boy in Spain received the therapy more recently and is not yet two years post-procedure, but is also doing well.)

Salzman said she is personally persuaded that the lentiviral vector is both safe and effective, converting enough nerve and brain cells to healthy function to make the outlook bright for these children. Her next goal is to expand clinical trials, both in Europe and in the U.S., treating enough patients to definitively show that gene therapy should be "the new standard of care for ALD." Once that happens, insurance companies will pay for the treatments and many more patients can be helped.

Donald B. Kohn, professor of Microbiology, Immunology, Molecular Genetics and Pediatrics at UCLA, warmly greeted the news from France. "Use of the lentiviral vector is a major milestone, advancing the technology," he said. The preliminary results indicate that 15-20 percent of the patients' nerve cells received the healthy genes, and that level of efficient gene transfer "is really unprecedented for a clinical trial."

Kohn, a leader in the gene therapy field, said we don't know why effectively treating far fewer than 100 percent of the nerve cells is sufficient to change the health of a patient, but one can speculate that the number of healthy cells making the proper enzymes is adequate to rescue the patient's other defective cells.

New Markets?

DEMAND FOR THE LENTIVIRAL VECTOR SEEMS DESTINED TO increase, as a number of other clinical trials involving other diseases get under way. Kohn was recently awarded a $9 million California Institute for Regenerative Medicine (CIRM) grant to develop a clinical gene therapy trial to treat sickle cell anemia using a lentivirus. He thinks the vector might also be suitable for gene therapy to treat other blood diseases and tissues in the eye.

"The work done by Dr. Verma and his team at the Salk was really pioneering, representing a quantum leap forward," Kohn said. And though it took a decade to go from lab to curing patients, Kohn called that "pretty quick" to address the "learning curve and testing" necessary for human use.

Verma is aware of a number of other clinical trials using the lentiviral vector, including two in London to treat Parkinson's Disease and Retinitis Pigmentosa, an hereditary cause of blindness. In the U.S. the vector is being used to treat SCID (Bubble Boy Disease) and a number of blood-based diseases including sickle cell and Chronic Granulomatous Disease (CGD), a group of hereditary diseases of the immune system.

Meanwhile, Amber Salzman, Eve Lapin and Rachel Salzman (now a freelance medical analyst who advises companies on diverse therapeutic areas) have an even broader agenda. They want to leverage a newborn screening initiative at the Kennedy Krieger Institute in Baltimore, MD to make it a routine requirement. Babies are not currently tested for ALD at birth and by the time it is diagnosed, it is often too late to help the children, she said. "Doctors won't screen for diseases for which they don't have known safe therapies," Salzman explained, and traditional bone marrow transplants are considered dangerous. She believes the use of gene therapy will change the treatment landscape and make routine testing worthwhile.

And while Salzman, her sisters and the French researchers all deserve major credit for the parts they have played in the ALD treatment story, Amber is quick to bring the focus back to Verma, saying it is "important that he be recognized" for both his tremendous scientific achievement and his interpersonal skills.

"He knows how to bring people together," Salzman said, marveling at Verma's particular ability to remember the names of her children and inquire about them. Not all scientists know how to get basic discoveries to patients, she said, but he can do it.

» WEB EXTRA

Patrick Aubourg Comments on Gene Therapy Success for Adrenoleukodystrophy (ALD)
www.salk.edu/insidesalk/genetherapy1

One on One with...
Bob Lizarraga

It's been said that a tour of the Salk Institute led by Project Manager **Bob Lizarraga** is one not to be missed. The stories he shares and the perspective he provides during the hour-long journey can only be told by someone who has been around long enough to experience them first hand.

> “...nobody now has the opportunity to see the inside of the empty lab buildings. It was a skin of concrete around a bunch of ribs that held everything in place.”
>
> – BOB LIZARRAGA

Bob Lizarraga, 1984

IN 1970, AFTER RETURNING FROM THE VIETNAM WAR and with some experience under his belt as a draftsman at an aerospace engineering company – Lizarraga walked onto the Salk campus at the advice of his mother, a UCSD professor of Latin American Studies who told him to look into trying to get a job “at that new Institute across the street.” With a full head of black hair stretching down to his lower back, he strolled into the Facilities office and landed an interview with Jonas Salk. It was the start of a 40-year career that came to an end in January when Lizarraga retired as the lead designer of building renovations. At age 65, he was ready to start a new chapter, but in retrospect, Lizarraga says working at the Institute had been the best experience of his life.

Tell me about your job interview with Jonas Salk.

First off, it was just amazing to have the opportunity to meet him. He told me about the overall concept of the Institute and how Facilities was considered to be a member of the team, as were the technicians in the lab. We were all working together toward the same end, which was scientific discovery. The Institute was looking for someone who could design gadgets that they needed in the lab, but couldn’t buy out of a catalogue. They had a machinist, but not someone who was skilled in design. So Dr. Salk hired me.

What sort of gadgets would you design?

For instance, there’s a thing called the hula shaker. The scientists wanted to take beakers with cells and oscillate them. So we came up with this platform that had a slow-speed motor, and we put an eccentric arm on it and connected it to the top plate. Then we anchored the four corners with tygon tubing from the labs. We made them here for a long time. But then there was a guy who worked in the lab and he went on to work for a company that sells lab equipment. He took one of these devices with him and within a week it was in the catalogue. That happened a few times over the years. There were times when our machinist couldn’t build what I drew, and he would tell me to build it. My dad was a master machinist, so I grew up around a machine shop. So I knew enough to make things, or just enough to get into trouble (laughs).

How did you make the transition from designing gadgets to reconfiguring lab space?

In the mid-to-late 1970s there was a higher demand for changes in lab space and less of a need for the gadgets. Dr. Salk wanted to change his lab, so that was one of the first drawings we did. Then Dr. (Renato) Dulbecco had a big tissue culture area that he wanted to redesign, so we did that. But it really took off when we started populating the south building. That was fun because nobody now has the opportunity to see the inside of the empty lab buildings. It was a skin of concrete around a bunch of ribs that held everything in place. It’s like a car or a plane, where you have harnesses, cables and tubing that are all part of this vehicle and you move components around inside of it. I looked at it as repackaging components that were meant to be moved around inside of the exterior shell. I thought of it as an engineering problem that needed a solution. At that point, I started studying design and architecture techniques on my own, which led me to where I’m now.

continued on next page...

That's precisely the philosophy behind why the buildings were designed the way they were, right?

That's right. The laboratories were outfitted in such a way so that they could be easily adapted to new configurations. All the interior partitions were not load-bearing so they could be dismantled or added to create new environments that lent themselves to the direction of the science. And as new technology was allowing the scientists to do their work in a different manner, the spaces within the building had to keep up with that and allow them the benefit of applying that new technology all within the confines of the concrete shell.

Who are some other people who made an impression on you at Salk?

Well, of course, there was **Francis Crick**. For instance, if Francis Crick and **Leslie Orgel** were sitting in the courtyard talking about the origins of life on earth, I could walk over to their table with my lunch tray and say, "Do you mind if I sit down?" They would say, "Oh certainly. Sit down." I wouldn't lend anything to the conversation, but I could listen to what they were saying and just be totally intrigued by what was going on. Ninety percent of it was going over my head, but there I was in the presence of these two remarkable men.

There was also a fellow here by the name of **Jacob Bronowski**. Even though he was a mathematician, he was very involved with the humanities. He wanted to study the effects of science on mankind, and while he was here, he finished his book, titled *The Ascent of Man*, which later became a film. He was like a walking encyclopedia. I got to know him because he would help me with some mathematical problems. But later I would just ask him questions. I've always been intrigued by my ancient heritage – the Aztecs and the Mayans. But I could speak with Bronowski about that kind of stuff, and he would give me his opinions. That was amazing. I would also ask him about bits and pieces from *The Ascent of Man*. And he would elaborate on that, too, or marvel at my stupidity (laughs).

Bob Holly was another one. He was a scientist who won the Nobel Prize, and he was an artist. Although I couldn't do it every day, I would go watch him sculpt things in clay that eventually became bronzes. Anything that struck my fancy, there was always someone here I could engage and get more information from. I came to find out that scientists are very gifted people who express themselves in many different ways.

Describe the work environment at Salk in the early days.

We were asked to become part of Dr. Salk's family, and that's exactly how it felt. We had regular meetings at least every two weeks. Keep in mind there were only 125 of us here at the time, so it was easy to gather everyone. We would be brought up to date on what was going on. We'd learn about new grants, new people who had been hired and all the things going on in the different laboratories. It was like in the ancient times when the tribes came together for their big pow-wow. We had an employees association then. And everyone at the Institute would give a dime for every $100 of their pay. So you gave like $2 per paycheck, but everyone did it. By the end of the month, we'd have

more than $500. So we'd have a Valentine's Day dance, a St. Patrick's dance, or a picnic. We would have an event every single month. Then we'd have volunteer staff members who would do the decorations, hire the dj, arrange for refreshments … we were a family.

What are some of your fondest memories of the Institute?

Being able to know everyone by their first name. I met Dr. Salk at my interview and I saw him at least once a day while he was here. But even after he left and he would come back infrequently, he never forgot my name. He knew about my parents, who they were and what they did. There was a point when I knew everybody's first name – even when we were up to 500 staff members. But as we got bigger, it became harder. Knowing everyone here, knowing who their kids were, or that they were going to college or that they got into the Army – that gave you a sense of unity and warmth.

Why are you retiring?

After 40 years, I think I've done my damage (laughs). Granted, I've learned a lot. I have truly been afforded the opportunity to grow here, and my life has become so much richer for it. My father worked until he was almost 75 years old and I saw him having to deal with going to work as an older man. I also saw him missing the opportunity to have a different richness in his life. I want to have a second life that's dedicated to just enriching myself in a whole different manner. So I want to stop, put this away and start a new chapter.

What will you miss most about working at the Salk?

This may sound contrived but, what I will miss the most is the daily challenges to perform at a high level of speed and accuracy. There has always been a lot of time to talk about ideas and projects but here at Salk, there is always a fixed deadline for completion or occupancy. As the talks and ideas and schemes drag on, the completion date does not. This inevitably always leaves little time to prepare drawings for the projects, yet the end result has to be correct and properly built. All this chaos can result in a tremendous sense of accomplishment at the end. When people say, "Thank you. It is just what I wanted," they have no idea how rewarding that simple statement can be.

> "The beauty of the scholars program is that it perpetuates the scientific process. It provides the opportunity for leading scientists like Jens to learn new techniques which he can take back to his lab, and we get new perspective from ideas he brings."
>
> – ANDY DILLIN

Jens Bruning

Glenn Center Scholars Program Opens Door to Sharing of Ideas

ALTHOUGH THEY BOTH CONDUCT RESEARCH ON THE INSULIN signaling pathway and its implications in disease, Jens Bruning says he had only met Salk scientist **Andy Dillin** once in his career. They may have shared a couple of e-mail exchanges a few years ago, but that was the extent of their communication.

Yet that didn't keep the German investigator from contacting Dillin in early 2009 to ask if he could work in his lab and collaborate at Salk.

"I was awarded a grant to study aging and age-related diseases as part of the German government's new initiative to promote more focused research rather than the traditional broad approach," says Bruning, who conducts research at the Institute for Genetics at the University of Cologne. "So I decided to contact Andy, who is well known for his work in this area."

The initial exchange eventually led to an invitation for a stint in the Dillin lab, where Bruning has been getting hands-on experience since August working with the *C. elegans* worm, a model organism in which Dillin demonstrated the mechanisms behind aging and its connection to Alzheimer's disease in 2006.

Dillin was able to extend the invitation through the visiting scholars program of the Glenn Center for Aging Research, which was established in January 2009 with a $5 million gift to the Institute by the Glenn Foundation for Medical Research.

Bruning became interested in basic research after receiving his medical degree and trained in endocrinology. His focus on diabetes led to postdoctoral studies at Boston's Joslin Diabetes Center. The experience solidified his decision to go into research.

A classically trained geneticist who until recently only worked with mouse models on diabetes research, Bruning says the *C. elegans* roundworm not only provides new opportunities for expanding his research but may also compliment his work in mice.

"The ease of genetic manipulation (in *C. elegans*) and its short lifespan really is a charm to find quick answers and to use it as a screening organism to then translate findings into higher model organisms such as mice," Bruning says.

"This experience is really giving me the opportunity to have stimulating discussions with other great (Salk) scientists like **Marc Montminy** to learn something completely new and develop new contacts. I think all of these things combined make this a really terrific program," he says.

The discussions and exchange of ideas is mutually beneficial, Bruning says. While Dillin offers suggestions on cellular pathways to investigate for potential new links in *C. elegans*, Bruning says he's sharing information on new mouse models his group has developed, which are of interest to Dillin as he expands his lab's repertoire of model organisms.

"The beauty of the scholars program is that it perpetuates the scientific process," says Dillin, director of the Glenn Center for Research Aging and an associate professor in the Molecular and Cell Biology Laboratory. "It provides the opportunity for leading scientists like Jens to learn new techniques which he can take back to his lab, and we get new perspective from ideas he brings."

Bruning agrees: "The environment in the lab is outstandingly welcoming and open to discussions. I think this is also a reflection of the philosophy at Salk."

> "It really will be a pleasure to lead and build upon a solid foundation that has been established over this event's 37-year history of success."
>
> – EDWIN T. HUNTER

Salk Prepares to Build on Annual Tax Seminar's Success

OVER THE LAST 37 YEARS, THE SALK Institute has provided an invaluable service to foundation managers by providing the latest tax law developments through its annual Tax Seminar. What started out as an intimate gathering, created by then Institute President **Frederic de Hoffmann**, has grown into a highly informative and comprehensive tax briefing for the non-profit community.

Today, it continues to draw representatives from many U.S. foundations, both large and small, including: The Ahmanson Foundation, the James Irvine Foundation, the Leona H. and Harry B. Helmsley Charitable Trust, the Bill & Melinda Gates Foundation, the Henry L. Guenther Foundation, the H.A. and Mary K. Chapman Charitable Foundations, and the Clayton Medical Research Foundation, among many others.

"The Tax Seminar has become a much-anticipated tradition at the Salk Institute," says Salk's Sr. Director of Foundation Relations **Seth Schechter**. "Aside from the opportunity to network and share ideas with one another, participants have the rare opportunity to hear from and ask questions of leading experts in private foundations over a three-day period."

The Institute is now gearing up for its 38th annual Tax Seminar, which is scheduled for May 12-14, 2010 at The Lodge of Torrey Pines in La Jolla. **Edwin K. Hunter**, a tax attorney with the firm of Hunter & Blazier (APLC) in Lake Charles, LA., and trustee for several charitable foundations, will chair the event, replacing Thomas J. Brorby, who stepped down as the seminar's chair last year.

"It really will be a pleasure to lead and build upon a solid foundation that has been established over this event's 37-year history of success," Hunter says. "As with any event that's been around as long as the Salk Tax Seminar, we are looking into ways to make it even more beneficial for those who attend."

What will remain intact, however, is the event's commitment to providing applicable information that benefits private foundations and unfettered access to experts in the field. Some of the tips that keep guests coming back each year include learning how to avoid pitfalls that lead to penalties, interpreting the latest tax and treasury regulations and understanding the impact to private foundations of proposed and pending legislation.

"The Salk Institute Tax Seminar is an excellent source for learning the complex and ever expanding IRS regulations that determine a private foundation's tax-exempt status," says Jerry Dickman, trustee for the H.A. and Mary K. Chapman Charitable Foundations.

"The seminar brings an exceptionally outstanding panel of foundation compliance experts to deal with the most current topics and provides invaluable opportunities to build relationships with other foundations executives," he says. "I believe annual attendance is a fundamental requirement of my responsibilities as a manger and trustee of private foundations."

SAVE THE DATE

First Annual Salk Golf Tournament

May 11, 2010 Del Mar Country Club

Proceeds benefit the Salk Institute
Info: 858-453-4100 x2062

Fred Dotzler

Linda Chester

Mary Jane Salk

Salk Institute Board of Trustees Elects Leaders in Venture Capital and Publishing to its Membership

THE BOARD OF TRUSTEES OF THE SALK INSTITUTE UNANIMOUSLY voted to elect three new members during its Nov. 13 meeting in La Jolla.

Fred Dotzler is co-founder and Managing Director of De Novo Ventures in Palo Alto, Calif. The company currently manages $650 million and invests in early stage medical device and biotechnology companies. During his career as a medical and biotechnology sector venture capitalist, Dotzler has invested in four companies that achieved market values greater than $1 billion. They include: San Diego-based Biosite (acquired by IMC), Inhale Therapeutic Systems, Omnicell, and Tularik Inc. (acquired by Amgen).

Prior to venture capital, Dotzler served in positions in marketing, finance, and operations for Searle, Millipore, Merrimack Laboratories, and IBM. Dotzler earned an MBA from the University of Chicago, a master's equivalent in Economics from the University of Louvain, Belgium, and a bachelor's degree in Engineering from Iowa State University, where he received a Professional Achievement Citation in Engineering in 2000.

The Salk Board of Trustees also elected literary agent **Linda Chester**. She begins her three-year term after having served as liaison to the Board for the Institute's International Council. Chester is founding president of the Linda Chester Literary Agency, which has bi-coastal offices (New York City and La Jolla, Calif.) and has represented many bestselling authors. Her agency represents a wide variety of adult literary and commercial fiction, as well as an array of non-fiction projects in areas that include science, business, finance, history, popular culture, spirituality, and biography.

Mary Jane Salk, who also comes from the publishing world, is replacing Chester as International Council liaison. She has served as editor of *Magazine Management* and editorial director of *Transworld Feature Syndicate*, an international magazine consortium. The widow of Dr. Lee Salk, brother to Dr. Jonas Salk, she is the author of five young adult books for Chelsea House Publishers, and was associate producer of the feature films *Goodbye, New York* and *Forever Lulu*.

She currently is a board member of several organizations, including Daytop Village Foundation, the oldest drug-free self-help program in the United States, and The Doe Fund, a cost-effective, holistic program that breaks the cycles of homelessness, addiction and criminal recidivism in New York City and Philadelphia.

Cycles of Feeding and Fasting Drive Circadian Gene Expression in the Liver

WHEN YOU EAT MAY BE JUST AS VITAL TO YOUR health as what you eat, researchers at the Salk Institute have discovered. Their experiments in mice revealed that the daily waxing and waning of thousands of genes in the liver—the body's metabolic clearinghouse—is mostly controlled by food intake and not by the body's circadian clock as conventional wisdom had it.

"If feeding time determines the activity of a large number of genes completely independent of the circadian clock, when you eat and fast each day will have a huge impact on your metabolism," says the study's leader **Satchidananda (Satchin) Panda**, an assistant professor in the Regulatory Biology Laboratory.

To investigate how much influence rhythmic food intake exerts over the hepatic circadian oscillator, graduate student and first author **Christopher Vollmers** put normal and clock-deficient mice on strictly controlled feeding and fasting schedules while monitoring gene expression across the whole genome.

They found that putting mice on a strict 8-hour feeding/16-hour fasting schedule restored the circadian transcription pattern of most metabolic genes in the liver of mice without a circadian clock. Conversely, during prolonged fasting, only a small subset of genes continued to be transcribed in a circadian pattern even with a functional circadian clock present.

In mammals, the circadian timing system is composed of a central circadian clock in the brain and subsidiary oscillators in most peripheral tissues. The master clock in the brain is set by light and determines the overall diurnal or nocturnal preference of an animal, including sleep-wake cycles and feeding behavior. The clocks in peripheral organs are largely insensitive to changes in the light regime. Instead, their phase and amplitude are affected by many factors including feeding time.

"The liver oscillator in particular helps the organism to adapt to a daily pattern of food availability by temporally tuning the activity of thousands of genes regulating metabolism and physiology," says Panda. "This regulation is very important, since the absence of a robust circadian clock predisposes the organism to various metabolic dysfunctions and diseases."

"Our study represents a seminal shift in how we think about circadian cycles," he says. "The circadian clock is no longer the sole driver of rhythms in gene function, instead the phase and amplitude of rhythmic gene function in the liver is determined by feeding and fasting periods—the more defined they are, the more robust the oscillations become."

Unraveling the Mechanisms Behind Organ Regeneration in Zebrafish

THE SEARCH FOR THE HOLY GRAIL OF REGENERATIVE MEDICINE—the ability to "grow back" a perfect body part when one is lost to injury or disease—has been under way for years, yet the steps involved in this seemingly magic process are still poorly understood.

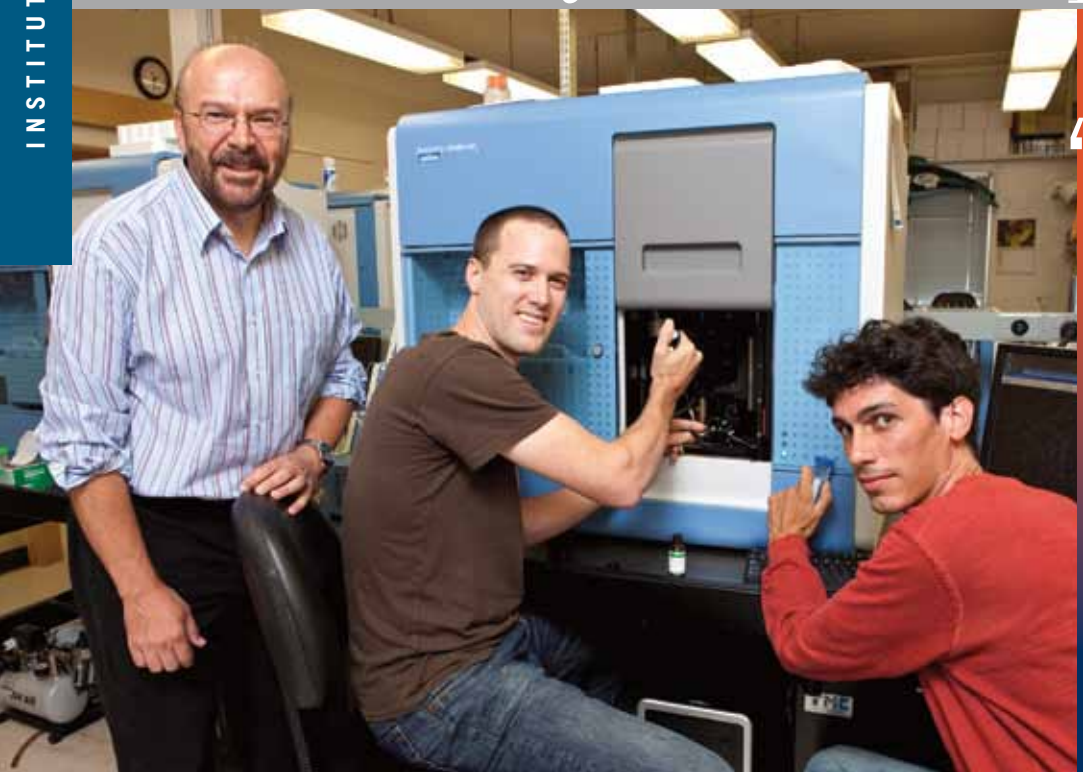
Now researchers at the Salk Institute have identified an essential cellular pathway in zebrafish that paves the way for limb regeneration by unlocking gene expression patterns last seen during embryonic development. They found that a process known as histone demethylation switches cells at the amputation site from an inactive to an active state, which turns on the genes required to build a copy of the lost limb.

"This is the first real molecular insight into what is happening during limb regeneration," says first author **Scott Stewart**, a postdoctoral researcher in the lab of **Juan Carlos Izpisúa Belmonte**, who led the Salk team. "Until now, how amputation is translated into gene activation has been like magic. Finally we have a handle on a process we can actually follow."

Their findings help explain how epimorphic regeneration—the regrowing of morphologically and functionally perfect copies of amputated limbs—is controlled, an important step toward understanding why certain animals can do it and we cannot.

"Our experiments show that normal development and limb regeneration are controlled by similar mechanisms," explains Izpisúa Belmonte, a professor in the Gene Expression Laboratory. "This finding will help us to ask more specific questions about mammalian limb regeneration: Are the same genes involved when we amputate a mammalian limb? If not, what would happen if we turned them on? And if we can affect these methylation marks in an amputated limb, what effect would that have?"

Discovery Roundup



> "Being able to study the epigenome in its entirety will lead to a better understanding of how genome function is regulated in health and disease, but also how gene expression is influenced by diet and the environment."
>
> –JOSEPH ECKER

Joseph Ecker, (from left) Ryan Lister and Mattia Pelizzola in the lab at the Salk Institute.

"TIME" Ranks Epigenome Study No. 2 Scientific Discovery of 2009

EACH OF THE 200 OR SO DIFFERENT TYPES of cells in our body—in the brain, the liver, the fat tissues—is handed the same basic instruction manual, yet somehow they all "see" a different set of instructions inscribed in the roughly 3 billion bases that make up the human genome. But it is the epigenome—a second layer of control beyond the regulation inherent in the sequence of the genes themselves—that controls which genes are accessible and when.

Some have compared it to the software run on the genomic hardware. "I can load Windows, if I want, on my Mac," says **Joseph Ecker**, professor and director of the Genomic Analysis Laboratory and a member of the San Diego Epigenome Center. "You're going to have the same chip in there, the same genome, but different software. And the outcome is a different cell type."

In a study "TIME" magazine recently ranked the second most important scientific discovery of 2009, Ecker and his team recently provided the first detailed map of the human genome.

"In the past we've been limited to viewing small snippets of the epigenome," says senior author Joseph Ecker. "Being able to study the epigenome in its entirety will lead to a better understanding of how genome function is regulated in health and disease but also how gene expression is influenced by diet and the environment."

Their study, published in the Oct. 14 advance online edition of *Nature*, compared the epigenomes of human embryonic stem cells and differentiated connective cells from the lung called fibroblasts, revealing a highly dynamic, yet tightly controlled, landscape of chemical signposts known as methyl-groups. The head-to-head comparison brought to light a novel DNA methylation pattern unique to stem cells, which may explain how stem cells establish and maintain their pluripotent state, the researchers say.

The emergence of epigenetics has already changed the way researchers think about how disease arises and how physicians treat it. Epigenetic changes play a crucial role in the development of cancer and some drugs that directly interact with the epigenome have been approved for the treatment of lymphoma and lung cancer and are now tested against a number of other cancer types.

"Unless we know how these drugs affect the entire epigenome, we don't really understand their full mechanism of action," says Ecker.

Recognizing the central role of the epigenome in many areas of biology and medicine, the National Institutes of Health launched a five-year Roadmap Epigenomics Program in 2008. The San Diego Epigenome Center, headed by Bing Ren, professor of Cellular and Molecular Medicine at the University of California, San Diego School of Medicine and head of the Laboratory of Gene Regulation at the Ludwig Institute for Cancer Research, is an integral part of the five year, $190 million push to accelerate research into modifications that alter genetic behavior across the human genome.

Umbilical Cord Blood a Source for Off-the-Shelf, Patient-Specific Stem Cells

UMBILICAL CORD BLOOD CELLS CAN SUCCESSFULLY BE REPROGRAMMED to function like embryonic stem cells, setting the basis for the creation of a comprehensive bank of tissue-matched, cord blood-derived induced pluripotent stem (iPS) cells for off-the-shelf applications, report researchers at the Salk Institute and the Center for Regenerative Medicine in Barcelona.

"Cord blood stem cells could serve as a safe, 'ready-to-use' source for the generation of iPS cells, since they are easily accessible, immunologically immature and quick to return to an embryonic stem cell-like state," says **Juan-Carlos Izpisúa Belmonte**, a professor in the Salk's Gene Expression Laboratory, who led the study published in the October issue of the journal *Cell Stem Cell*.

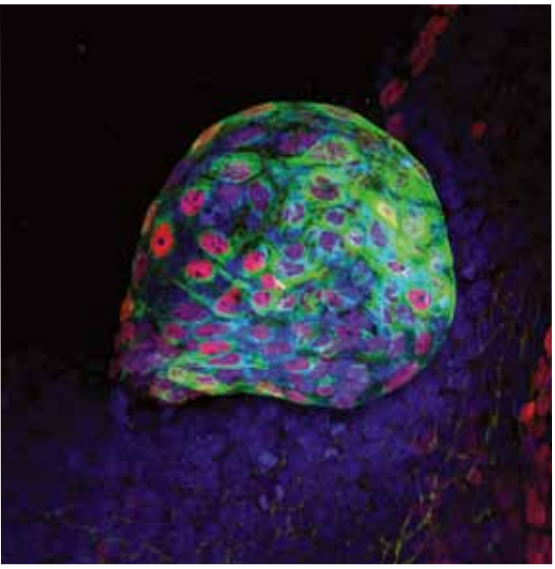
Worldwide, there are already more than 400,000 cord blood units banked along with immunological information. Due to their early origin, cells found in umbilical cord blood contain a minimal number of somatic mutations and possess the immunological immaturity of newborn cells, allowing the Human leukocyte antigen (HLA) donor-recipient match to be less than perfect without the risk of immune rejection of the transplant.

HLA typing is used to match patients and donors for bone marrow or cord blood transplants. HLAs are special surface markers found on most cells in the body and help the immune system to distinguish between "self" and "non-self."

"Selecting common HLA haplotypes from among already banked cord blood units to create iPS cell would significantly reduce the number of cell lines needed to provide a HLA match for a large percentage of the population," says Izpisúa Belmonte.

Since the first adult cells were converted into iPS cells, they have generated a lot excitement as an uncontroversial alternative to embryonic stem cells and as a potential source for patient-specific stem cells. Unfortunately, taking a patient's cells back in time is not only costly, but could be difficult when those cells are needed right away to mend injured spinal cords or treat acute diseases, and outright impossible when the effects of aging or chronic disease have irrevocably damaged the pool of somatic cells.

With this in mind, Belmonte and his colleagues set out to transform hematopoietic stem cells isolated from cord blood into iPS cells. They not only successfully converted them using only two out of the four most commonly used factors—OCT4 and SOX2—but also in less time than any other previously published methodology require. No matter, whether the researchers started with freshly collected cord blood or previously frozen samples, the resulting iPS cells were indistinguishable from human embryonic stem cells.



The endodermal layer, identified here by markers AFP and FoxA2, gives rise to the digestive tract, lungs and bladder.

Delaying the Aging Process Protects Against Alzheimer's Disease

AGING IS THE SINGLE GREATEST RISK factor for Alzheimer's disease. In their latest study,researchers led by **Andrew Dillin**, associate professor in the Salk Institute Molecular and Cell Biology Laboratory, found that simply slowing the aging process in mice prone to develop Alzheimer's disease prevented their brains from turning into a neuronal wasteland.

Published in *Cell*, their finding is the latest clue in Salk scientists' quest to shed light on the question of whether Alzheimer's disease onset late in life is a disastrous consequence of the aging process itself or whether the beta amyloid aggregates that cause the disease simply take a long time to form.

"In this study, we went directly to the root cause of Alzheimer's disease and asked whether we could influence the onset of the disease by modulating the aging process," says first author Ehud Cohen.

To answer this intriguing question, he slowed the aging process in a mouse model for Alzheimer's by lowering the activity of the IGF-1 signaling pathway, which plays a crucial role in the regulation of lifespan and youthfulness across many species. As a result, mice with reduced IGF-1 signaling lived up to 35 percent longer than normal mice.

Cohen then employed a battery of behavioral tests and concluded that chronologically old but biologically young animals appeared nearly normal long after age-matched, normal-aging Alzheimer's mice exhibited severe impairments in their ability to find a submerged platform in the Morris water maze or stay atop a revolving Rota Rod.

"Our study opens up a whole new avenue of looking at the disease," says Dillin, a Howard Hughes Medical Investigator. "Going forward, looking at the way we age may actually have more impact on the treatment and prevention of Alzheimer's disease than studying the basic biology of the disease itself.

"This work is a celebration for the entire field of aging researchers, as it validates the long-held hypothesis that genetic and pharmacologic changes to create a healthy lifespan, or 'healthspan,' can greatly reduce the onset of some of the most devastating diseases that afflict mankind," he adds.

Inder Verma Receives Spector Prize, Gates Foundation Grant

INDER VERMA, A PROFESSOR IN the Laboratory of Genetics and the Irwin Mark Jacobs Chair in Exemplary Life Science, will receive the 2010 Spector Prize in honor of his work in developing an HIV-based vector for use in gene therapy.

Awarded by the department of Ophthalmology at Columbia University and co-sponsored this year by the department of Genetics, the prize recognizes the contributions of Abraham Spector, the Malcolm P. Aldrich Emeritus Research Professor who was a leading figure in eye research.

Verma is the third recipient of the prize, which is intended to honor outstanding basic research that has made fundamental contributions to elucidating cell biology and that provides the basis for designing approaches for controlling and curing disease.

In related news, Verma was among a group of researchers who received a $100,000 grant from the Bill & Melinda Gates Foundation in October to develop a mouse model of human malaria. The model will serve as a new tool for evaluating strategies to fight the disease, including testing critically needed new anti-malarial drugs and vaccines as well as testing for long-term toxicity of anti-malarial therapies.

Postdocs Honored with Fellowships from Salk's Center for Nutritional Genomics

SIX POSTDOCS HAVE RECEIVED A TOTAL OF $360,000 in grants through the Salk Center for Nutritional Genomics Fellowship Program to support research in diabetes and metabolism. The award provides each scientist with $60,000 to cover salary, lab supplies and equipment over the next year.

The Institute established the Salk Center for Nutritional Genomics with a $5.5 million gift from the Leona H. and Harry B. Helmsley Charitable Trust in April 2009. The Center employs a molecular approach to nutrition and its impact on the role of metabolism on the immune system, cancer, diabetes and lifespan, thereby increasing the understanding of how nutrients affect health.

Capitalizing on the Salk's strength in collaborative research, the Center draws expertise from leading laboratories at the Institute to deepen its diabetes research with the intent to unravel the mechanisms that modulate the body's energy balance and the factors that set the stage for metabolic disease.

The recipients of the fellowships, the institutions where they graduated and the Salk lab where they work are:

Weiwei Fan, University of California at Irvine (2008), Ronald Evans Laboratory; **Bing Luan**, Chinese Academy of Sciences (2008), Marc Montminy Laboratory; **Erin Quan Toyama**, University of California at San Francisco (2009), Reuben Shaw Laboratory; **Mark Huising**, Radboud University Nijmegen (2006), Wylie Vale Laboratory; **Yeddula Narayana**, Indian Institute of Science (2008), Inder Verma Laboratory; **Nathan Baird**, University of Oregon (2008), Andrew Dillin Laboratory.

Fred H. Gage Elected to the European Molecular Biology Organization

FRED H. GAGE, A PROFESSOR in the Laboratory for Genetics at the Salk Institute and the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases, is one of only three Americans elected an Associate Member to the European Molecular Biology Organization (EMBO) in 2009.

"The election once again puts a spotlight on the most outstanding representatives of the current generation of life scientists. We look forward to the fresh impulses this exceptional group will bring to our organization," said EMBO Director Hermann Bujard.

Gage's laboratory concentrates on the adult central nervous system and unexpected plasticity and adaptability to environmental stimulation that remains throughout the life of all mammals. He and his colleagues showed that, contrary to accepted dogma, human beings are capable of growing new nerve cells throughout life.

Small populations of immature nerve cells are found in the adult mammalian brain, which are generated in a process called neurogenesis. Gage is working to understand how these cells can be induced to become mature functioning nerve cells in the adult brain and spinal cord.

His lab also showed that environmental enrichment and physical exercise can enhance the growth of new brain cells and his team is studying the underlying cellular and molecular mechanisms that may be harnessed to repair the aged and damaged brain and spinal cord.

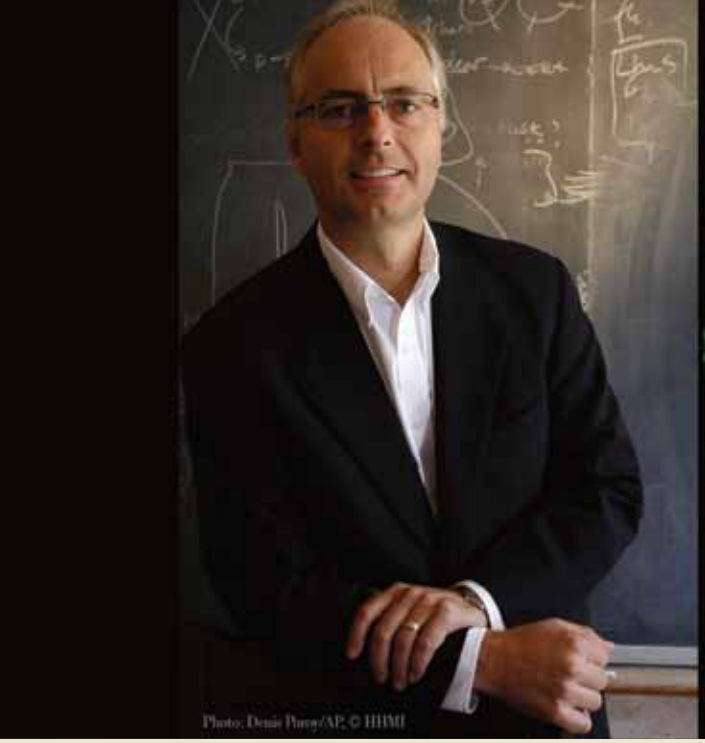
Clodagh O'Shea Receives Sontag Foundation's Distinguished Scientist Award

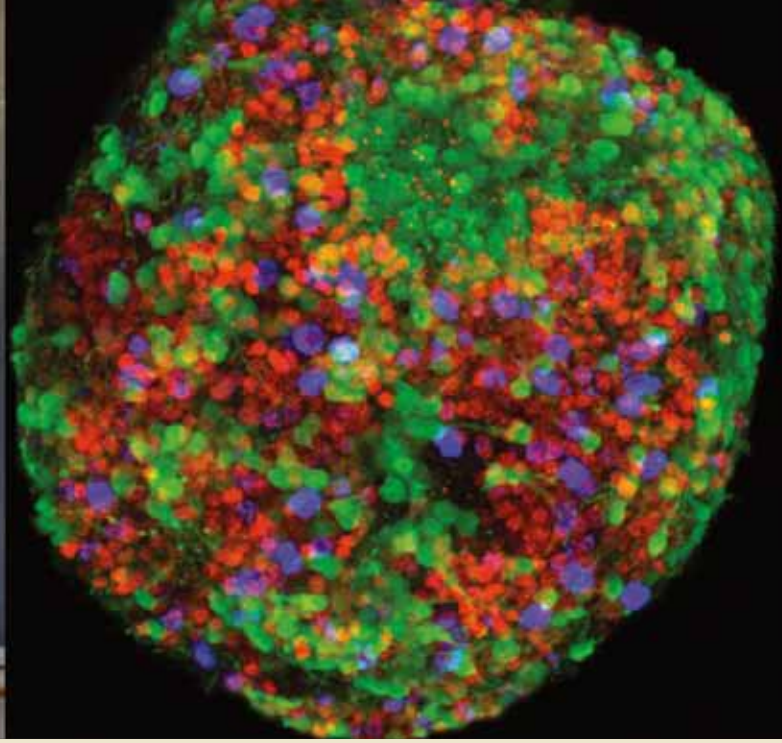
CLODAGH O'SHEA, AN assistant professor in the Molecular Cell and Biology Laboratory, has been selected by The Sontag Foundation to receive the 2009 Distinguished Scientist Award. She will receive $600,000 over a four-year period to develop new viral therapies to treat invariably fatal glioblastomas and other brain tumors.

Through the prestigious Distinguished Scientist Awards, The Sontag Foundation recognizes and supports the work of outstanding early career scientists whose research has the potential to generate new knowledge relating to causes, cures or treatment of brain tumors.

"The Sontag Foundation wants to get people with fresh ideas to think about brain cancer in novel ways," says O'Shea. "I have not focused on brain cancer until I came to the Salk and breaking into the field would have been very difficult without their support. I am extremely excited to be able to translate the genetic understanding of brain cancer into transformative treatments for patients suffering from this terrible disease. To achieve this we will combine new viral vectors, tools and mouse models in a way that's never been done before. It's high risk but it really could change things."

O'Shea is an expert on so-called oncolytic viruses that act as tumor-mutation-guided missiles, which target tumor cells for their own purposes. When infected, cells burst open to release thousands of viral progeny. The next generation of viruses can seek out remaining tumor cells and distant micro-metastases.





CIRM Awards Samuel L. Pfaff $15.6 Million to Develop Stem Cell-Based ALS Therapy

SALK RESEARCHER SAMUEL L. PFAFF HAS been awarded a $15.6 million grant by the California Institute for Regenerative Medicine (CIRM) for translational research focusing on developing a novel stem cell-based therapy for Amyotrophic Lateral Sclerosis (ALS) – or Lou Gehrig's Disease.

Pfaff, a professor in the Salk's Gene Expression Laboratory and an investigator for the Howard Hughes Medical Institute, will lead the group of researchers who will work on the four-year project, which marks the first CIRM funding explicitly expected to result in FDA approval for clinical trials.

The research team will focus on astrocytes, the star-shaped support cells that provide nutrients for nearby motor neurons. Working with six different lines of human embryonic stem cells (hESC), the team will grow clinical-grade astrocyte precursor cells and identify the line that is best suited for implantation in laboratory models.

They hypothesize that the transplanted human astrocyte precursors (hAP) will mature into astrocytes in vivo and provide support for diseased spinal motor neurons. Astrocytes are also capable of clearing excess neurotoxic glutamate and could thereby slow or halt the progression of ALS by preventing motor neuron degeneration.

Once the astrocyte precursors are tested for efficacy and safety to minimize the possibility of tumorigenesis, the next step will be to move forward with human clinical trials after approval by the FDA, says Pfaff.

"This team grant is a natural fit for San Diego because it capitalizes on the strength of neuromuscular disease research from the local scientific community," says Pfaff. "The standard has been set very high on this project because we are aiming to grow a safe population of astrocytes that can be introduced into patients. Our success will be measured by whether it will help extend the lives of patients suffering from ALS."

Martin Hetzer Wins 2009 Aging Research Award

MARTIN HETZER, HEARST ENDOWMENT ASSOCIATE professor in the Salk Institute's Molecular and Cell Biology Laboratory, has received a 2009 Senior Scholar Award in Aging from the Ellison Medical Foundation. He will receive $150,000 a year for four years to study the mechanisms at work in nuclear pore complexes, channels that mediate molecular traffic between the nucleus and cytoplasm of cells.

Changes in gene activity are part of the cellular aging process; however, the mechanisms that cause age-related alterations in gene expression are poorly understood. Hetzer has recently discovered that nuclear pore complexes, essential channels that shuttle molecules across the nuclear membrane, are extremely long-lived in non-dividing cells and deteriorate over time, causing cytoplasmic proteins to "leak" into the nucleus in neurons.

Because most of the cells in our bodies are non-dividing, he hypothesizes that this deterioration might be a general aging mechanism leading to age-related defects in nuclear function, such as the loss of youthful gene expression programs. His lab has observed filaments of the cytoplasmic protein tubulin inside the nuclei of old mouse and rat neurons, for example, a phenomenon that has been linked to various neurological disorders, including Parkinson's disease. Based on this finding, he speculates that the deterioration of nuclear pore complexes over time might initiate or contribute to the onset of certain neurodegenerative diseases.

Hetzer will use the Ellison funding to investigate the molecular mechanisms that lead to the observed damage and loss of the proteins that make up the nuclear pore complexes. He also plans to study the physiological consequences of leaky nuclei for cell function and to analyze the consequences of defective nuclear pore complexes in gene expression.

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Salk **Calendar**

FEBRUARY 2010

4 Renato Dulbecco Nobel Lecture
11 Stem Cells and Cancer Symposium
18 Leslie Orgel Memorial Lecture

MARCH 2010

24 A Taste of Discovery Supper
25 Francis Crick Nobel Lecture

APRIL 2010: 50th Anniversary Celebration Begins

13 A Taste of Discovery New York
20 The San Diego Cell Biology Meeting
23–28 Chihuly at Salk - Watch for Details

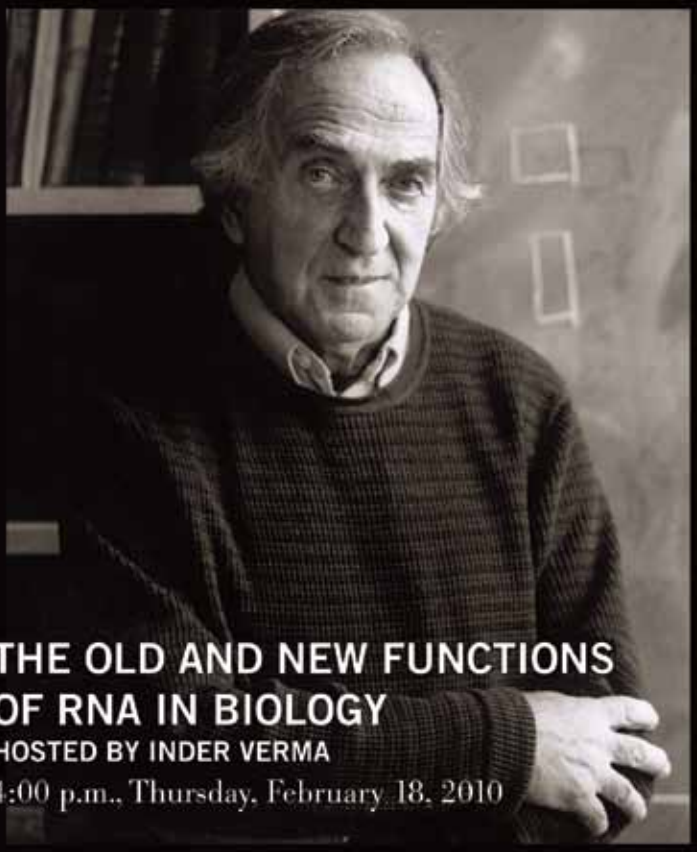
MAY 2010

11 First Annual Salk Golf Tournament
12-14 38th Annual Tax Seminar on Private Foundations

50

CELEBRATING FIVE DECADES OF SCIENTIFIC EXCELLENCE IN BASIC RESEARCH. [1960 –2010]

The Third Annual
Leslie Orgel Memorial Lecture



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Institute Professor
David H. Koch Institute for Integrative Cancer Research
Massachusetts Institute of Technology
Nobel Laureate in Physiology or Medicine, 1993