People & Ideas

Rusty Gage: A plastic approach to neuroscience

Gage's work focuses on neurogenesis and plasticity in the adult central nervous system.

Rusty Gage

Fred "Rusty" Gage studies flexibility in the adult brain. His research has shed light on neuronal diversity and contributed greatly to the field of neuroplasticity. Gage's success may be due in part to his own adaptability. Throughout his career he has remained open to unusual ideas and new opportunities, demonstrating that the human brain is capable of generating nerve cells throughout life and that genetic mobile elements are active in neural progenitors.

As the son of a Navy pilot, Gage lived all over until he was 11 years old: Virginia, California, Chicago, Hawaii, and Naples, Italy. His father eventually retired from the Navy and became a stock broker for Merrill Lynch. The family settled in Frankfurt, Germany and considered it home for the next 18 years.

Gage then worked at the University of Florida for three years, did his graduate work at Johns Hopkins, and became an assistant professor at Texas Christian University. Before his current position at the Salk Institute, he spent time as an associate professor at the University of Lund in Sweden and as a professor at the University of California, San Diego. Although his work has taken him throughout the world and covered a range of scientific fields, his interest in the mechanisms of central nervous system (CNS) repair has remained consistent. We contacted him to learn more.

> "At least in a few adult brain areas, the most profound form of neuroplasticity happens throughout life."

When did your interest in science begin? What was your first experience of science?

My older sister was a scientist and always encouraged me by sending me science books, articles, and letters of encouragement. My first real experience with research came at the end of my freshman year in college at the University of Florida, where I took a summer job doing electrophysiology experiments on models of epilepsy propagation in rodents. The Isaacson lab was a very active and supportive environment, with undergrads, graduate students, and postdocs all working together.

Where and with whom have you studied?

After working in Bob Isaacson's lab for three years at UF, I went to Johns Hopkins University to do my graduate work with Dave Olton, who parenthetically had been a grad student with Bob at the University of Michigan. I received my master's degree and PhD at JHU when I was 25 in 1975. I did not do a postdoc initially but took an assistant professorship at TCU in a joint multidisciplinary program between psychology, chemistry, and biology. There weren't many neuroscience programs at that time.

It was at this time that the discipline of neuroscience was beginning to form. After a few very good years of research, I realized that I needed more training and applied for a Fulbright Fellowship to work with Anders Björklund in Lund. Those were good years: 1981–1985. Not only was the science productive and fun but my wife, Mary Lynn, and I integrated into Lund and Swedish society, learning the language and culture and developing lasting friendships. And our two daughters, Francesca and Alexandra, were born in Lund during that period.

What interested you about your current area of study?

I have always been interested in structural and functional plasticity. As an undergrad, I worked on the electrophysiological and anatomical bases of genetic and induced epilepsy. In graduate school and the years afterward, I worked on the behavioral, anatomical, and chemical aspects of recovery following focal brain damage. In Sweden, I continued to work on CNS repair after damage, with a focus on the newly discovered neurotrophic factors, as well as on developing new neural transplant techniques and strategies to probe CNS plasticity (1). My ongoing work on adult neurogenesis is a natural extension of that early work, as we continue to search for mechanisms and procedures to induce CNS repair (2). The adult neurogenesis research has shown that, at least in a few adult brain areas, the most profound form of neuroplasticity happens throughout life. So if we can understand how the brain allows new neurons to be born and integrate into a complex circuit like the hippocampus, those rules and mechanisms may be extended to other brain areas that lack this robust form of plasticity (3).

What are you currently working on? What is up next for you?

In 2002, while studying the transcriptional signature of adult neural progenitors, we inadvertently discovered that mobile elements, in particular line elements (L1) and

Text and Interview by Kimberly Siletti
ksiletti@rockefeller.edu

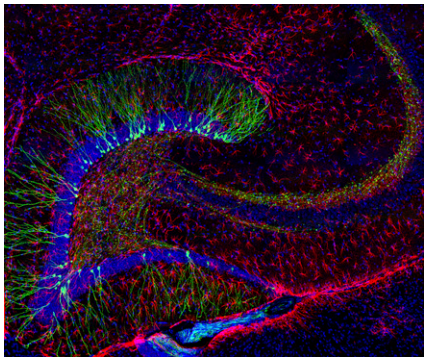

IMAGE COURTESY RUSTY GAGE

Two-month-old neurons in a four-month-old mouse. Green is GFP, which labels a population of newborn cells. Red color shows astrocytes, which are supporting cells that play essential roles for the proper function of the nervous system. Blue color shows DAPI-stained nuclei.

IAPs (a rodent-specific form), were active in neural progenitors and participated in creating what is now called somatic mosaicism in the brain (4). The concept of somatic mosaicism is based on the growing appreciation that, contrary to previous beliefs, each neuron in the adult brain is genetically different from every other neuron. We continue to study somatic mosaicism, searching for the mechanisms as well as the functions or consequences of this genomic reorganization. I must say that I resonated to somatic mosaicism as yet another form of structural plasticity (5). This area of research will drive me and the lab for some time to come.

What kind of approach do you bring to your work?

I am an optimist. Forty-five years of experience in the lab have helped me realize that most things don't work out as planned or hypothesized. However, even the mistakes and seemingly blind alleys can lead to discoveries and new ways of thinking that are fun and interesting. I have always enjoyed learning new areas of science and incorporating that knowledge as best I can into the problems I am currently working on.

What did you learn during your PhD and postdoc that helped prepare you for being a group leader?

I learned the value of being surrounded by smart, highly motivated people at all levels. The variety of ideas and skills that I absorbed in those years helped expand the scope of my research and better impart knowledge to my own lab. In particular, I came to appreciate the major contribution made by highly skilled staff members; some of my most important staff members have been with me for over 30 years.

What has been the biggest accomplishment in your career so far?

In addition to my genetic family, I have a lab family, the generations of students and trainees who have moved through the Gage lab. Many of them have established successful careers of their own, yet they keep in touch, attending regular "Gage Lab Meetings" that feature current lab members and past lab members. Best of all, they bring their students and *their* students, sharing data and new ideas in a supportive and stimulating environment.

What has been the biggest challenge so far?

I think the biggest challenge was the pushback we received when we began our work on adult neurogenesis in the hippocampus and proposed that the parental progenitor cells in the dentate gyrus were, in fact, giving rise to functional neurons. Resistance was present every step of the way. However, I think that the long battle for acceptance toughened me up a bit for a later challenge, when we showed L1 activity in neural progenitor cells. While the debate is over as to whether there is genetic mobility in neural progenitors, the mechanism, magnitude and function of this mobility are yet to be fully revealed.

Who were your key influences early in your career?

Bob Isaacson, who supported me working in his lab starting at 18 years of age (and who died recently); Dave Olton, who died too young in 1994; Warren Torgerson, who introduced me to principal components analysis and multidimensional scaling; Sol Snyder, a hero at Johns Hopkins; and Anders Björklund, friend and mentor; et al.

What is the best advice you have been given?

"You are lucky to be a scientist; enjoy it."

What hobbies do you have?

Running, exercise, squash, cooking, drawing, playing musical instruments (poorly), and, once upon a time, martial arts.

What do you think you would be if you were not a scientist?

I have no idea. I entered college as a philosophy major, but the die was cast to be a scientist so long ago. I have lots of interests and could have probably enjoyed other careers, though perhaps not as much.

"Forty-five years of experience in the lab have helped me realize that most things don't work out as planned or hypothesized."

What has been your biggest accomplishment outside of the lab?

Having a family that apparently still loves me.

Any tips for a successful research career?

Don't plan too far in advance; be open to new opportunities and ways of looking at the world.

1. Gage, F.H., A. Björklund, and U. Stenevi. 1984. *Nature*. 308:637–639.
2. Gonçalves, J.T., S. Schafer, and F. Gage. 2016. *Cell*. 167:897–914.
3. Eriksson, P.S., et al. 1998. *Nat. Med.* 4:1313–1317.
4. Muotri, A.R., et al. 2005. *Nature*. 435:903–910.
5. McConnell, M.J. 2013. *Science*. 342:632–637.

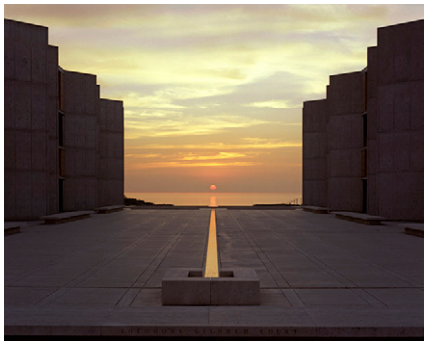

PHOTO COURTESY JOE BELCOVSON

The Salk Institute (Vernal Equinox)