
From football player to neuroscientist:
Sam Young has had an astonishing career.

Photo: O'Donnell Agency – Jennifer Sullivan

Still Scoring **Touchdowns**

In college they called him Stump – as in tree stump – because of his physique and his strong will. Today, former football player **Samuel Young** is a renowned neuroscientist. Using innovative tools and sophisticated techniques, he would like to find out how nerve cells communicate with one another. The head of a junior research group at the **Max Planck Florida Institute** is the quintessential researcher. But his career took an unconventional path.

TEXT **HUBERTUS BREUER**

Samuel Young doesn't look like someone to be messed with. The man is muscular and built like a tank, and his loud laugh confidently marks out his territory. Sitting under the palm trees on the campus of Florida Atlantic University, eating steak and fries, and hearing how he came from a middle-class neighborhood in New Jersey to head a junior research group at the Max Planck Florida Institute, one gets the impression that his physical presence and sheer strength of will were instrumental in his achievements. After all, nothing was handed to this young scientist on a plate.

For a little over a year now, 37-year-old Samuel (Sam) Young has been a researcher in Jupiter, on the Atlantic coast of Florida. He is researching how neurons communicate with one another. He tackles his work with an innovative arsenal of tools, such as manipulated viruses that insert genes into cells, and sophisticated surgical techniques that allow him to manipulate the gene functions of certain brain cells in mice and rats in order to study their neuronal signal transduction.

RESEARCHING THE BRAIN WITH VIRUSES

The researcher developed these tools himself at such academic centers as Princeton University, the University of North Carolina in Chapel Hill, the Salk Institute in La Jolla, California, and the Max Planck Institute for Biophysical Chemistry in Göttingen. "What I do is basic research – we want to know what biophysical and molecular mechanisms underlie brain function. Once we understand these basic mechanisms, we will then be able to understand the causes of brain disease," he says.

Young's career could not have been foreseen when he embarked on his studies – from party-loving college stu-

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dent and football player to outstanding researcher in the fields of molecular biology, virology, electrophysiology and biophysics. The scientist remembers something his mentor, cancer researcher Arnold Levine, told him: Young had just graduated from Princeton and Levine remarked that people like him didn't really exist in the sciences.

Sam Young grew up in New Jersey, in a typical American suburban town – Caldwell, about 16 miles from New York. Home was a two-story, colonial-style house with a driveway and a garden in the back. When Sam was a child, his mother worked Friday and Saturday nights as a waitress and later became a full-time housewife. She only returned to work when he was in high school. She finally earned a college degree two years ago, at the age of 60. His father was a sales representative for Frito-Lay, delivering potato chips and snack foods in neighboring Newark, a city with a notorious reputation – drug-related crime, gang wars and muggings were commonplace. One day, Young's father was attacked and shot, and took early retirement as a result. "My father was a highly intelligent man, but unfortunately, he didn't have the same educational opportunities that he made sure his children had."

A GOOD EDUCATION FOR A GOOD START

Young's father strongly encouraged his children to get a good education: "You need to get an education. You don't want to have to be doing hard physical work like me to earn a living." Sam and his siblings took his words to heart. His older brother, Andrew, was the first person in his family to graduate from college. He now works in the pharmaceutical industry. His younger brother has a doctorate in chemistry and works as a senior research chemist in the area of green energy technology.

"It's hard for me to say this now," says Sam Young as he takes a break from his meal, "but my father beat us when we were young. That instilled in me a certain amount of insecurity. At the same time, my father's beatings made me tougher and able to withstand physical and mental punishment." Moreover, Sam Young was always well built and a good athlete. "I had the feeling that nothing could break me. I always thought that I could survive anything."

Young also excelled at school: "I never had to study. Everything came to me very easily," he recalls. He discovered his affinity for science at an early age, too. One of his favorite books was *Science Experiments You Can Eat.* He learned how cabbage can detect acid, how bacteria make yoghurt and how sugar turns to caramel.

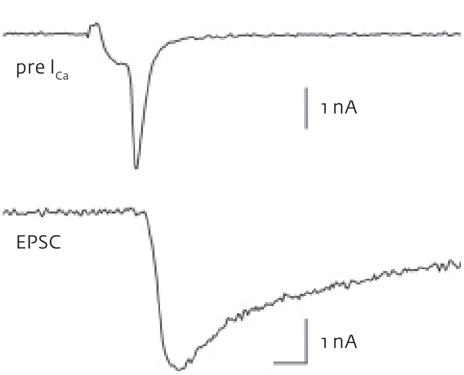
When he went to high school, he began playing football. Young wasn't the biggest player on the team – 5'10" (178 cm) in this sport tends to be below average – but he was strong and fearless. His reputation as a talented player

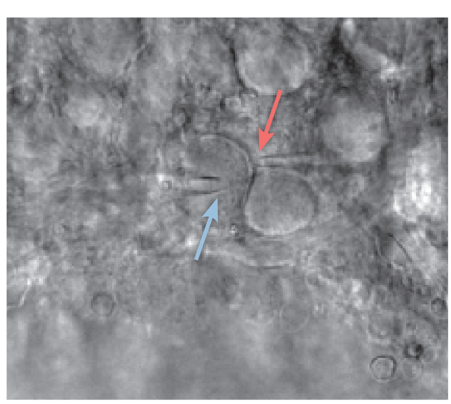
In the patch clamp method, a fine glass pipette is placed on the cell membrane of a nerve cell to measure electrical current in the neurons.

left | Flow of current through a calcium channel in the presynaptic cell (top); flow of current in the postsynaptic part of the synapse (bottom) (nA: nanoamp; ms: millisecond)

center | Simultaneous measurement at the presynaptic (red arrow) and postsynaptic part (blue arrow) of a calyx of Held synapse.

right | Sam Young aspirates the cell membrane. The vacuum causes the edges of the pipette to adhere to the membrane.





Graphics: Max Planck Florida Institute; photos: Max Planck Florida Institute (center), O'Donnell Agency – Jennifer Sullivan (right)

Sam Young checks to see how an experiment is progressing. Fluorescent nerve cells can be seen on the screen in the background beside the microscope.

Photo: O'Donnell Agency – Jennifer Sullivan

helped him in his college applications. Of all places, it was the elite Princeton University that was grateful to welcome the football player with excellent grades in its incoming college class. For Young, it was confirmation of his belief that he could do anything.

SNOBBERY AND PREJUDICE

Princeton was a culture shock; the majority of his classmates came from wealthy families who had attended private schools and had every advantage that such environments offered. All of them were destined, from the day they were born, to attend an Ivy League university. "Initially, I had major problems with the elitism on campus." Classmates made him and other football players feel that they had been accepted at Princeton merely because of their sporting skills. Naturally, that created a strong bond among the football players, and Young soon found a home within the football team.

Young began his first semester with an experiment: "Because I always performed well in the natural sciences, I wanted to see what would happen if I attended seminars only in the humanities. As it turned out, that wasn't such a good idea." All the while, he was partying hard, just like many American college students living away from home for the first time. Young indulged excessively in the initiation rites that mark the passage into the world of young adulthood. "I was the one who always did something crazy at a party. Most of my fellow students didn't even know my real name. To them I was simply 'Stump'" – as in tree stump, the man who is as wide as he is tall and doesn't move for anything or anybody.

When he again turned his attention to the natural sciences, he decided to major in molecular biology. When he approached the secretary in the department, she simply looked at him and said: "There are no football players in our department." However, one of the stars in the field of molecular biology, cancer researcher Arnold Levine, was himself a football fan and took Young under his wing. "If it wasn't for Arnie Levine giving me a chance, I probably wouldn't be a scientist today," says Young. Levine was famous as the co-discoverer of the protein p53, which suppresses the development of cancer in some tumors. He accepted that Young would be unable to work in the lab during the football season, but he could count on him twice as much for the rest of the time. He assigned Dan Notterman to be Young's adviser. The molecular biologist had worked with

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Levine to investigate whether p53 was also instrumental in preventing the formation of cells with abnormal chromosome numbers. In 1998, two years after he graduated from college, Young published the results as co-author in the leading cancer journal ONCOGENE.

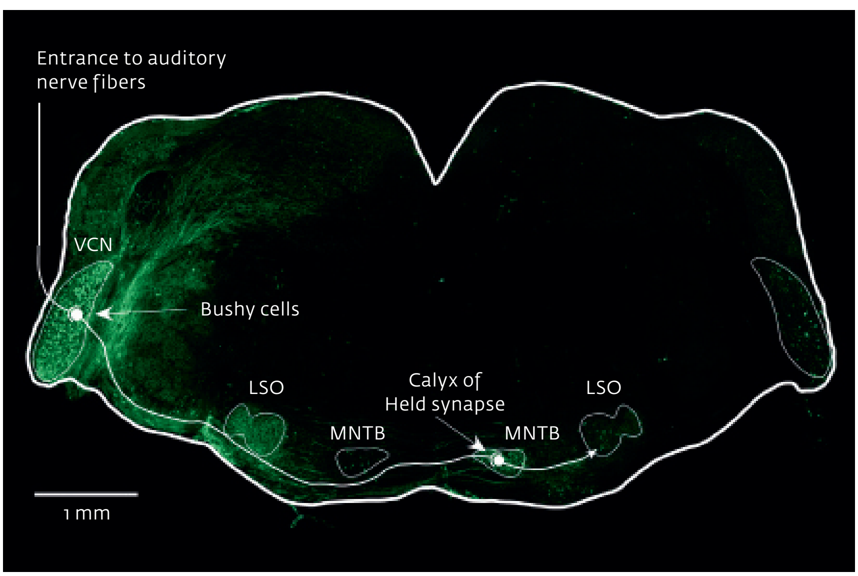
During his last year in Princeton, the young scientist heard two lectures that would have a crucial influence on his career: one on the potential of gene therapy, and another on the study of memory in fruit flies. Young's decision to do his doctorate with a pioneer of viral gene therapy and co-creator of gene therapy vectors, Jude Samulski at the University of North Carolina in Chapel Hill, paved the way for his scientific career.

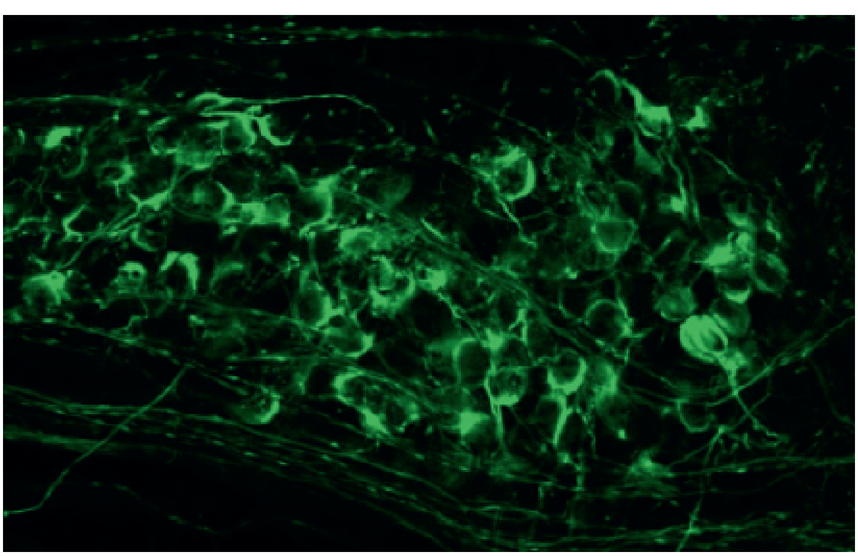
On his own initiative and at his own expense, Sam Young began working in Samulski's lab immediately after he graduated. He soon had his own project: investigating how adeno-associated viruses (AAV) are integrated in the genetic makeup. The advantage of these viruses is that, as far as is known, they don't cause genetic disorders. When they are inserted into a human cell, they integrate themselves into chromosome 19.

In his dissertation, Young examined the specific mechanism by which these viruses install themselves in this particular location in the human genome. To do this, he had to learn new skills: cloning, developing new cell lines and producing recombinant viruses. During his time with Samulski, he also learned how to write a paper and deliver a presentation. "Jude taught me from the ground up how to be a scientist."

SLOW AND STEADY WINS THE RACE

One of the areas that Sam Young investigated was the number of AAV proteins expressed in a cell. He initially approached the project in his own

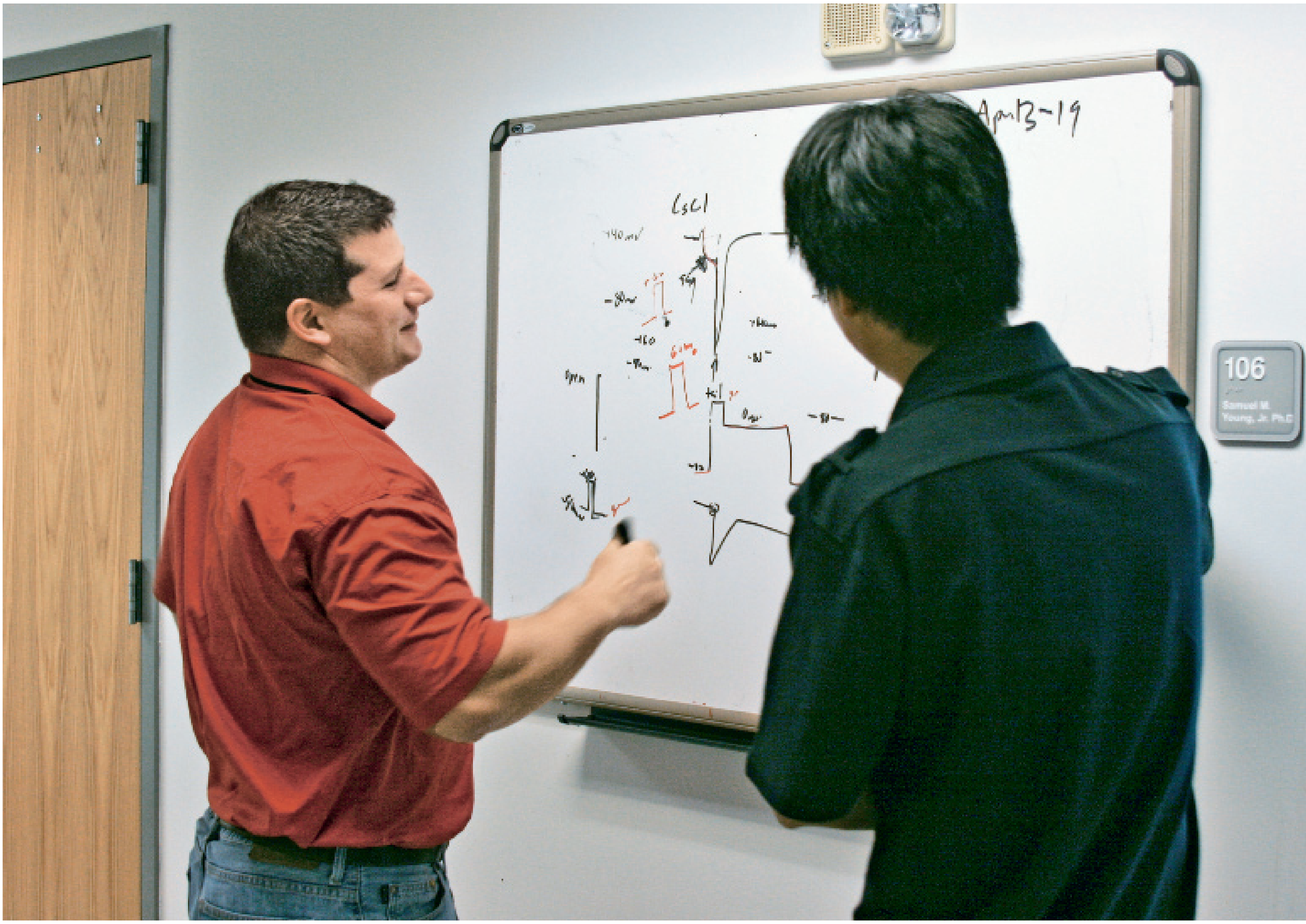




top: Relay in the auditory brainstem system of an 11-day-old mouse (the associated brain areas are outlined in white). Using a virus, the nerve cells were genetically modified in such a way that they form a fluorescent protein and are illuminated in green. Information transmitted through the calyx of Held synapse helps the animal localize sound. (VCN: ventral cochlear nucleus, LSO: lateral superior olive, MNTB: medial nucleus of the trapezoid body).

bottom: Calyx of Held synapses, greatly magnified. At this stage of development, the synapses are cup-shaped.

Photos: Max Planck Florida Institute



Science also needs teamwork: Sam Young doesn't analyze American football plays anymore. These days, his focus is on ion flows and changes in potential.

way. With hard work and determination, he was looking for a quick "touchdown" – to publish a paper as lead author – in just his second year of graduate studies. However, in order to quickly finish what he thought was the final experiment, he accepted sloppiness in trade. "What I tried to do was garbage science," he now admits. Samulski reacted accordingly and threw Young out of his lab. "There are no shortcuts in science."

In retrospect, Sam Young sees this as the turning point in his young career. When he returned to the lab three weeks later, he had radically changed his attitude. "It was a cathartic moment. And I always remember Samulski's advice: 'Sam, you'll never have enough time to do it right the first time, but you'll always have enough time to do it again.'" Years later, in recognition and respect for everything Samulski had done for him in and outside the lab, Young named his first son Jude.

Young completed his doctorate three and a half years after completing his bachelor's degree. He discovered that the AAV integrated itself on chromosome 19 not only because it found suitable docking sites there, but because its proteins also supported chromosome replication during cell division.

HOW DO LEARNING AND MEMORY WORK?

Once he had completed this project, Young began looking around for a postdoctoral position. He didn't want to stay in gene therapy, as the issues were too applied for him – he was interested in basic research. He remembered his fascination with the neuronal basics of memory and wondered whether neuronal genes could be manipulated in such a way that conclusions could be drawn about their function.

Brain research, however, had not exactly been waiting for Sam Young. Some researchers told him that his idea was too ambitious. Nevertheless, neurobiologist Charles Stevens at the Salk Institute for Biological Studies in San Diego was interested. "I will always be grateful to Stevens for giving me the opportunity to switch fields," says Young today. He had to learn a new research field from scratch. He spent the first six months studying Eric Kandel's classic textbook on the neurological principles of memory and Bertil Hille's definitive work on ion channels in cell membranes. Steve Heinemann, another expert in molecular neuroscience at Salk Institute, also supported Young in exploring what was, for him, unfamiliar territory. The risk he took in working in a new field demonstrates one of Young's strengths: he doesn't shy away from acquiring a new skill, even if it serves to answer just one scientific question. "I never aspired to work across disciplines – it was simply the inevitable result of my research interests," he recalls. >

Photo: O'Donnell Agency – Jennifer Sullivan

Sam Young always has his work tools from a previous life at hand: a football on the shelf and a pair of cleats under the desk.

Sam Young also learned the complex patch clamp technique. This is a method that uses fine pipette tips to measure the smallest currents through the individual ion channels of a cell membrane. This method was developed by biophysicists Bert Sakmann and Erwin Neher in the 1970s at the Max Planck Institute for Biophysical Chemistry in Göttingen. In 1991, both of them received the Nobel Prize in Physiology or Medicine for their work. Bert Sakmann is the Founding Director at the Max Planck Florida Institute.

The patch clamp technique is used to investigate how synaptic contacts, and consequently the efficiency of signal transmission, change. At the synapse, the electrical signal that moves through the neurons is converted into a chemical signal, since it must be sent from the transmitter neuron to the recipient neuron. This process occurs by means of neurotransmitters, which are packed in membrane-bound sacs (vesicles). They must fuse with the cell membrane before they reach the synaptic cleft between the transmitter and the recipient. So-called SNARE proteins, which Sam Young studied in greater detail in La Jolla, play a role in this process. He established that they evidently have a strong influence on signal strength. Contrary to what was previously believed, this is not dependent on the number of vesicles at the cell membrane. Young worked on the project for four years and, in 2005, summarized his findings in a paper published in the prestigious scientific journal PNAS.

IN THE NOBEL PRIZE WINNER'S LABORATORY

Sam Young's stay in California was followed by a second postdoctoral position in Germany, where he also later became an internal group leader – with Erwin Neher at the Max Planck Institute for Biophysical Chemistry in Göttingen. Young had met Neher at a conference in the summer of 2004, where Neher had suggested collaborating. In reply, Young daringly asked: "How about if I join your research group?" Neher, who receives hundreds of requests every month, spontaneously answered "Great idea!" The Nobel Prize winner remembers the conversation well. "Sam Young had virology expertise, which we needed in the lab at that time. His time in the lab of my earlier mentor Charles Stevens also ensured that he had an in-depth knowledge of electrophysiology."

However, a small problem soon arose for Young. A few weeks after his meeting with Erwin Neher, he met the love of his life, Sidney, at a party. For two months, he remained silent about his impending departure. When he told her about his plans, the new relationship threatened to fall apart. However, after a few dramatic crisis meetings, they agreed that she would not only go with him, but that they would also get married – which, however, took another three years.

In addition, Young had never been to Germany before, or anywhere else in Europe. "I wasn't aware how far north it is – at least compared to New Jersey, where I grew up." As much as the cooler climate surprised him, Young still considers Göttingen, and Neher's department in particular, to be the Shangri-la of science – that legendary paradise in the Himalayas where people devote themselves entirely to a spiritual existence.

In Neher's lab, Young began working, for the first time, with the synapse that would be central to his work right

Photos: Max Planck Florida Institute (3)

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up to the present day: the calyx of Held, a huge synapse in the auditory brainstem of rats and mice, which can measure up to 0.02 mm in diameter. Once again, the researcher was entering uncharted territory. He had to create new technology and develop special recombinant adenoviruses. At the same time, he developed a surgical method that allowed him to specifically inject the recombinant viruses into the calyx of Held in the auditory brainstem of newborn rats. This meant that he could use the viruses as transport vehicles to insert new genes into the nerve cells and thus manipulate molecular processes at the synapse and obtain information about how they worked.

LAST-MINUTE SUCCESS

For the first two years, not one of his experiments worked. Then, in 2007, at lunch with Erwin Neher one day, Young revealed that, if the next experiment did not work, the entire project would be a failure. Meanwhile, his wife was five months pregnant. As a responsible family man, Young was anxious to achieve success, which would also secure his future career. Everything depended on whether the foreign genes that he inserted into the calyx synapse by means of viruses would be activated at a level that would disrupt the molecular processes there.

He wanted to conduct the crucial experiment before his daughter was born. But just as he was about to take the first electrophysiological measurement, the micromanipulator broke. He had to wait another few weeks before announcing that he had successfully manipulated the synaptic function. The scientist discovered that Synaptotagmin, a protein localized in the cell membrane, helps position synaptic vesicles at the active zone and co-facilitates their simultaneous release.

Before the paper was published, Young once again had to think about his future and had discussions with several universities in the US. “My home and my family’s home are in the States, so staying in Germany was not an option.” But he was not completely lost to the country – an opportunity unexpectedly arose to apply for the position to head a junior research group at the newly founded Max Planck Florida Institute. “The opportunities that Max Planck offers – without the pressure of having to constantly write research applications or teach too much – and the ideals for which Max Planck stands, were very attractive,” says Sam Young. “I was already very familiar with the Max Planck ecosystem from Göttingen, and the new institute gave me the opportunity to continue working within the Max Planck family.”

Using the tools that he developed himself, Young embarked on the task of further unraveling the precision engineering of synaptic signal transduction. His viral gene shuttles allow him to genetically manipulate neurons; his innovative surgical methods and the patch clamp technique help him to take precise measurements. He wants to use these methods and tools to examine a number of other issues in greater detail: how the vesicles and neurotransmitters become functional, what role selected proteins play in this process, and how the pre-synaptic calcium channels are arranged at the active zone. “We have to perform both quantitative measurements and molecular manipulations, as this is the only way we can develop accurate models of how synapses function,” says the researcher.

He is also working with Florida Atlantic University to develop a graduate program in neurosciences there, and has already organized a neuroscience symposium at which the graduate program was launched. “We can establish something special here,” he says cheerfully. This writer is convinced that the program will be a success. Sam Young has the determination to make it one. ◂

GLOSSARY

Adenoviruses
A group of viruses that can infect human and animal cells. They find their way into the cell interior in membrane-bound sacs. Adenoviruses don’t have a viral envelope and are highly resistant. Scientists often use them to insert genes into somatic cells. In humans, naturally occurring adenoviruses can cause infections such as respiratory or gastro-intestinal infections.

Ion channels
Channel-shaped proteins in the cell membranes through which electrically charged particles such as sodium, calcium or chloride ions can flow in or out. Various triggers can change the physical structure of the protein, with the result that the channel becomes permeable or blocked. These include electrical and mechanical stress, binding partners and light. Ion channels are crucial in determining the electrical properties of a cell.

Viral gene therapy
Viral gene therapy is used to cure genetic diseases. The viruses are used as vehicles to insert a functioning version of the defective gene in certain cells. The genetically modified viruses can infect cells but cannot multiply further.