The Source Code of Life

Eugene W. Myers never attended a biology lecture. Nevertheless, he made a career for himself in this field, and by developing a computer program, made a major contribution to decoding the human genome. The bioinformatician has recently become a Director at the **Max Planck Institute for Molecular Cell Biology and Genetics** and at the Center for Systems Biology in Dresden.

TEXT **ELKE MAIER**

Eugene W. Myers, new Director at the Max Planck Institute for Molecular Cell Biology and Genetics, played a decisive role in sequencing the human genome.

Photo: Sven Döring

» Only in the last ten years have scientists been able to make each protein visible and watch what happens in a living cell live through the microscope.

Deep in concentration, Eugene W. Myers sits in front of the computer monitor, his glasses on his forehead. He has one e-mail to send before turning his full attention to his visitor. His austere office is on the second floor of the Max Planck Institute for Molecular Cell Biology and Genetics in Dresden. The message he has just typed is for Klaus Tschira in Heidelberg.

The new Center for Systems Biology, to which Eugene – "Gene" – W. Myers was appointed Director six months ago, was established by the Max Planck Society jointly with the Klaus Tschira Foundation and the Max Planck Foundation. It is a joint project run by the Dresden-based Max Planck Institutes for Molecular Cell Biology and Genetics, and Physics of Complex Systems. Its function is to develop methods to improve our understanding of the sequences that take place in animate nature.

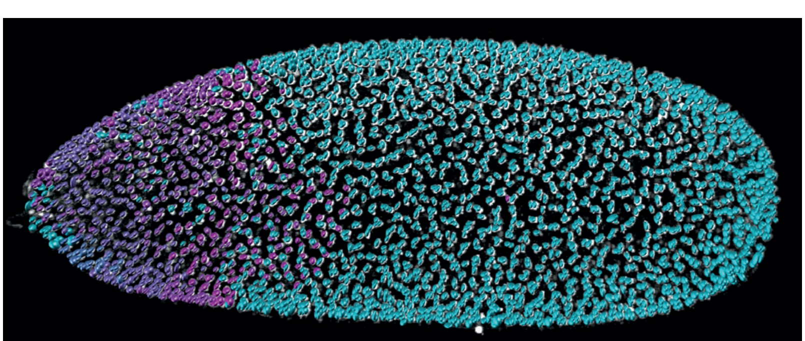
Wearing jeans, a white shirt topped with a black jacket, with graying, wavy hair and dark eyes, Gene Myers looks a bit like Hollywood actor Richard Gere. Gene Myers is famous, too – not on screen, but in bioinformatics, a discipline in which he is a pioneer. Around the turn of the millennium, he made a decisive advance in decoding the human genome. The BLAST software that he co-developed in 1990 is used by researchers the world over to compare DNA sequences. He has already received numerous awards, including the Max Planck Research Prize 2004; the journal Genome Technology even named him as the most influential bioinformatician.

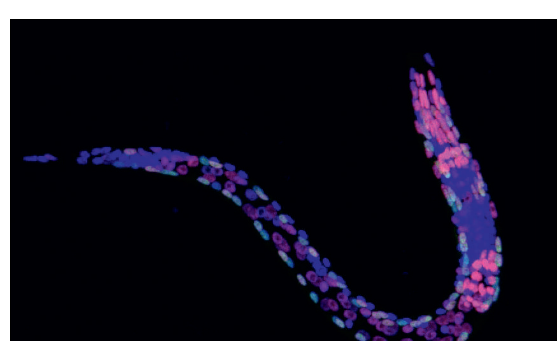
FROM SEQUENCE ANALYSIS TO MICROSCOPY

Gene Myers is a passionate coffee drinker. Consequently, he suggests that we move to the cafeteria in the lobby of the institute, where he gets himself a cappuccino and settles himself at one of the metal bistro tables. His speech is punctuated now and again with German expressions, which he emphasizes with vigorous gesturing, particularly when something excites him. This happens often – especially when he explains how, after years of sequence analysis, he came upon microscopy.

"It was in 2003 when I visited the Max Planck Institute," he explains, sipping his cappuccino. "Tony Hyman showed me some video recordings of a cell dividing. I could see exactly how the spindle apparatus was formed and how the chromosome halves divided equally between the two daughter cells. I was fascinated," he says, enthusiastically. "You could see the tubular spindle proteins grow, each individual microtubule. Until then, I had no idea what you could see with a microscope!"

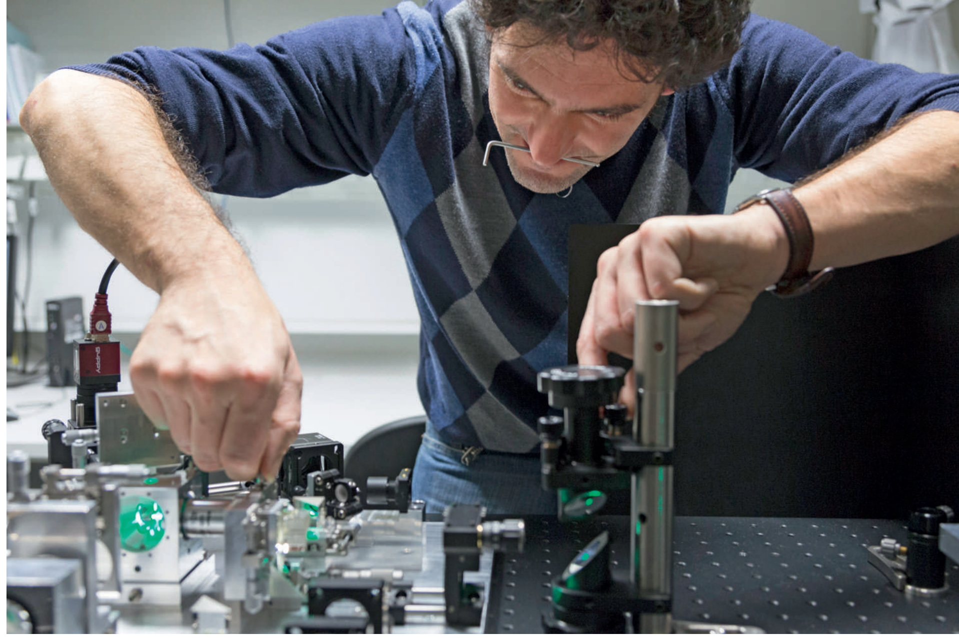
It has only recently been possible to record such images. "It's only been about ten years since we gained the ability to make each of the proteins in a cell visible with the aid of fluorescent dyes," Myers explains. In this way, scientists can now watch what happens in a living cell live through the microscope. For Gene Myers, who at the time was working at the University of California in Berkeley, the film shot by the researchers in Dresden was a crucial experience. Until then, he had been concerned primarily with the alphabetic code of the genome, developing computer programs to compare genetic se-

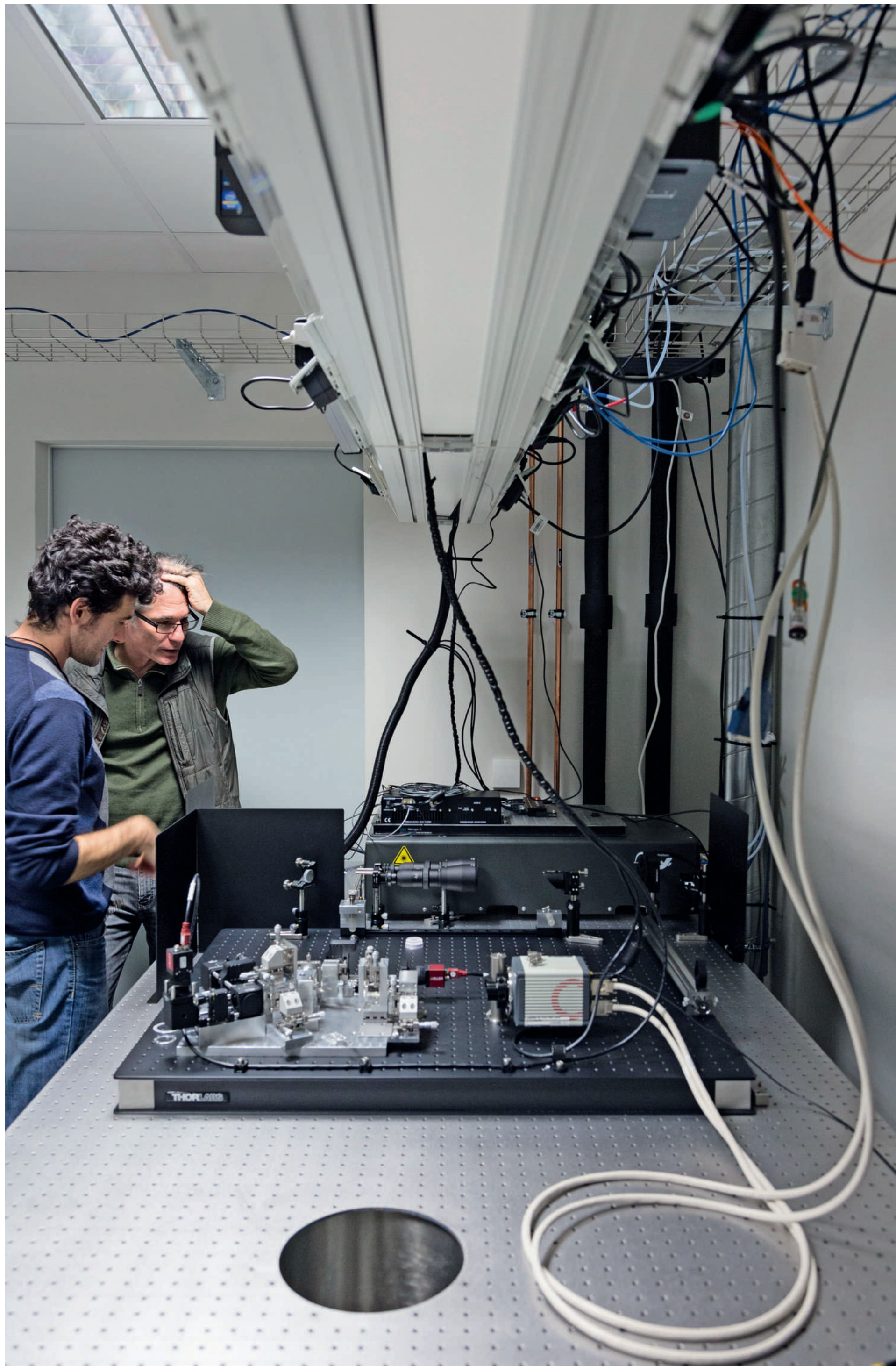




Using groups of cells, such as these from a *Drosophila* embryo (left) or the larvae of the threadworm *Caenorhabditis elegans* (right), the researchers are able to see every detail of the cell divisions and gene expression.

Photos: Gene Myers (2)





Top: Microscopes made to measure. Gene Myers and his colleagues in Dresden are developing two microscopes simultaneously. Scientist Nicola Maghelli is seen here making some fine adjustments to obtain the optimum resolution.

Bottom: In the optics room, Gene Myers and Nicola Maghelli discuss how the excitation beam should be adjusted – a question that is clearly hard to answer.

quences. Since then, his focus has shifted to what is written in this code. "I want to know how genetics produce the diverse forms that life takes. For example, how do genes determine how the brain of the *Drosophila* fruit fly is wired, and how it actually works?"

3-D IMAGES COMPILED FROM COUNTLESS INDIVIDUAL PHOTOS

The fruit fly's brain is barely more than a third of a millimeter in size. Yet it consists of 100,000 nerve cells. It takes enormous effort and expense to investigate such tiny structures – special high-resolution microscopes and sophisticated algorithms to translate countless individual images into a three-dimensional image.

For example, it took two years for Gene Myers and his then colleagues at the Howard Hughes Medical Institute in the US to develop a multi-photon microscope that enabled them to study the brain of a mouse. "A task that previously took a year and a half could now be done in six days – and the images were much sharper," says Myers.

With this experience behind him, he is now aiming to develop two high-resolution microscopes in parallel at the institute in Dresden: one to reveal the processes in the interior of cells; the other to investigate groups of cells. "We will then, for instance, be able to follow

Photos: Sven Döring (2)

exactly what happens in the *Drosophila* embryo," the scientist explains. "How do cells communicate with one another? How do they collaborate to produce a fly?"

UNDERSTANDING THE ORGANISM AS A WHOLE

It is this interdisciplinary research approach to understanding the organism as a whole that Gene Myers appreciates at the institute in Dresden. "That, and the fact that the Max Planck Society also allows its scientists the freedom to try new things and take risks." Ultimately, however, it wasn't just the research environment that attracted him to Germany. "Dresden is beautiful, and my wife and I enjoy the culture and the way of life."

Long walks along the banks of the Elbe with his Border Collie crossbreed Poème are as much a part of the lifestyle for him as the daily commute to the institute by bicycle. Important, too, are the friendships that have developed with his fellow scientists in Dresden. The term friendship crops up regularly during our conversation – the legacy, perhaps, of a childhood on the move.

Born in Boise, Idaho, Gene Myers soon found himself travelling far and wide. His father was an employee of oil giant Exxon and worked in various countries in Asia. The family – his mother, who was French by birth, an older sister and younger brother – always accompanied him.

Gene Myers discusses the day's program with his secretary Sabine Jochen. Despite his tight schedule, he likes to have enough time for his colleagues and lend a hand himself.

Photo: Sven Döring

» Back in 1979, bioinformatics didn't have a name as such. The subject was still in its infancy. Gene Myers was soon to go a long way toward changing all that.

German lesson: Klaus Thiel from the Goethe Institute helps Gene Myers practice the use of the genitive. In his new home country, it's important to him that he soon be able to communicate in German.

Describing an adventurous childhood spent in Pakistan, India, Indonesia, Hong Kong and Japan, he says, "I celebrated my first birthday onboard ship on the way to Karachi, and my brother was born in India. We never stayed longer than two or three years in one place. It was hard to keep leaving friends behind." On the other hand, he acquired insight into various cultures and ways of life, and learned to adapt to new circumstances.

The family's middle child began at a very early age to show a marked predilection for figures. He had barely learned to count at the age of four, when he began to write down all the numbers from 1 to 1,000. However, little Gene's talent initially went unrecognized. "According to my report cards, I had a gift for art. There's no mention of mathematics."

Mathematics was his favorite subject, but he also developed a broad interest in the sciences. "I read all sorts of things, like biochemist and science fiction author Isaac Asimov," he recalls as he stirs his second cappuccino. Gray's Anatomy, the standard work in anatomy, also made a huge impression on him. At the age of 12, he knew that he wanted to be a researcher.

THE MATHEMATICS STUDENT SKIPPED TWO SEMESTERS

Toward the end of his time at high school, the family returned to the US. Gene Myers enrolled to study mathematics at the renowned California Institute of Technology, and promptly skipped the first two semesters. As his second subject, he chose electrical engineering. However, there was one certificate that, to this day, is still outstanding: "I was supposed to take a course in rhetoric, but I was too shy to speak in public," he explains with a grin. "And anyway, I thought that later on, as a scientist, I wouldn't need it." A mistake, as he now knows. But even without a course in rhetoric, today, he has no trouble fascinating people with his ideas.

Gene Myers first came into contact with bioinformatics in 1979 while studying for his doctorate under Andrzej Ehrenfeucht at the University of Colorado. "In those days, the subject didn't have a name. It was still in its infancy," says Myers. He himself was soon to go a long way toward changing all that.

In 1985 – Gene Myers was an assistant professor at the University of Arizona by this time – he was developing a program to compare text files when a colleague came up with the idea that something similar could be suitable for the alphabetic code of DNA, and stirred his enthusiasm for bioinformatics. But his reason for working on a biological subject wasn't solely scientific in nature: "Unlike the informaticians, the biologists always had something to celebrate," he says with a mischievous grin. "We had a lot of fun!"

He began to work closely with Webb Miller at Penn State University and David Lipman, who was Director at the then new National Center for Biotechnology Information. Their cooperation

Photo: Sven Döring

Two's company. While Gene Myers ponders over a program code in the evening, his Border Collie crossbreed Poème likes to get comfortable on the sofa.

Portrait of a globe trotter. A photo of Gene Myers with his nursemaid Lilly in Calcutta. A large part of his childhood was spent in various Asian countries, where his father worked for oil giant Exxon.

laid the foundation for the software program BLAST. Since it was first published in 1990, the program – which is freely available on the Internet – has been cited around 40,000 times, making it one of the most frequently cited scientific works. BLAST has even made its way into the language of the laboratory: when biologists are comparing DNA sequences by computer, the term they use is "blasting."

It was via DNA analysis that Gene Myers finally came upon the most exciting project of his scientific career: sequencing the human genome. The size alone – 3.2 billion base pairs – presented researchers with a huge challenge, as long strings of DNA can't be decoded in one piece. Generally, the sequence becomes too imprecise after around 800 bases, or breaks off. Scientists are thus compelled to work their way forward step by step.

THE TASK: TO COMPLETE A 50-MILLION-PIECE PUZZLE

The quickest way is called shotgun sequencing, in which the DNA is duplicated and then – as in a shotgun blast – fragmented into small snippets. These are then sequenced before being reassembled by computer. As with a jigsaw puzzle, the more pieces there are, the more difficult the task becomes. The human genetic puzzle has around 50 million pieces.

"When we proposed to shotgun-sequence the human genome, most people thought it was a crazy idea," Gene

Photos: Private (2)

» Thanks to Myers' program and the shotgun method, the sequencing was completed years ahead of the deadline that had been set and at only a tenth of the cost.

Myers recalls. 2,000 snippets of DNA was considered to be the upper limit; any more would exceed the computer's capacity. An article outlining the procedure was accordingly turned down by the most important journals, NATURE and SCIENCE. The GENOME RESEARCH journal was willing to publish it, but only on the condition that a critical article appeared alongside it.

One of those who firmly believed in the shotgun procedure from the very beginning was Craig Venter. When, in 1998, he established his company Celera, which was working on sequencing the human genetic profile in parallel with the publicly funded Human Genome Project, he offered Gene Myers a job. Myers now had to prove that his method worked, not only in computer simulations, but also in reality. "That was the most stressful time of my life, but also the most exciting," he recalls.

Visit to the White House: Gene Myers (third from left) is seen here with Samuel Broder, former Director at the National Cancer Institute, biochemist and Nobel laureate Hamilton Smith, and Craig Venter, founder of the company Celera (from left).

Photo: Private

With hundreds of millions of dollars at stake, the pressure to succeed was huge. Gene Myers worked like a man possessed, writing endless lines of computer code. But he kept going. Thanks to his program and the shotgun method, the sequencing was completed years ahead of the target date and at only a tenth of the scheduled cost. Now, at last, even the most rigid skeptics were silenced.

Myers is now in the process of setting up a new research group in Dresden: four post-docs and a doctoral student are already working with him, and there's room for more. Then again, he has no wish to expand too far. It's important to him to remain involved in the work being done by every individual. "Twelve would be the right size," he muses.

A PASSION FOR WRITING PROGRAMS

Gene Myers can't imagine leading his team from behind a desk. He's too much a man of action, too hands-on. Despite his many tasks, he still does his own programming as often as possible: first thing in the morning with the obligatory cappuccino in hand, and occasionally at night or on a plane. "I just love writing program code!"

One last cup, then Gene Myers must head off for his next meeting. "Putting a research group together, organizing our life in Dresden – it's all very exciting," he concludes. At the moment, he and his wife Daphne are living out of a suitcase until their new home by the Elbe is ready for them to move into. Another building is also in the planning stage: it is due to be built beside the Institute for Cell Biology and Genetics, and will house the Center for Systems Biology with its three research groups.

This winter, Gene Myers intends to allow himself some time out in the Canadian Rocky Mountains. Deep snow skiing is another of his passions. Maybe because it's a little like science: another opportunity to explore untouched terrain and leave a trail behind. ◄