



**“For me, Pioneering is ...**  
Prof. Stefan Hell

Living up to Life

**Leica**  
MICROSYSTEMS

Our interview partner on the topic of Pioneering is Prof. Stefan Hell, a scientific member of the Max Planck Society and director at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, where he heads the Department of Nanobiophotonics. In addition to further chairs and memberships, he is also head of the High Resolution Optical Microscopy research group, a partnership department of the German Cancer Research Center (DFKZ).



... to be the first to see the direction of the stream of insight, and to play a small part in determining its future course.”

Professor Hell, you are a pioneer of far-field optical microscopy beyond the diffraction limit. Do you have a natural penchant for physics and optics, or did your interest arise later, in school or at university? Was there a specific event that triggered it?

As a child, I already had a fascination for the rules of nature – those hidden, yet essentially simple laws that govern everything. I was thrilled to get to know them in detail while studying physics. They let us make sequences of events predictable – to a remarkable degree, at any rate. To this very day, I find that well-written physics textbooks make for compelling reading – even if I already know the end of the story. And if your edifice of ideas is sound, you can apply it to inventions that have practical value and which are also significant outside the realm of physics. The path from the frontiers of discovery to practical application remains exciting to me. My teachers in school and at university encouraged that fascination and directly or indirectly helped me realize my pleasure in it. But looking back, I have to say that I've been fascinated with exploring the inner workings of things for as long as I can remember.

Before we talk about the personal significance that pioneering spirit has for you, could you briefly tell us about the current focus of your research?

That's easy. I'm still working on building the sharpest light microscopes ever. And they should not only be sharp, but also bright and fast, to make them suitable for the broadest range of applications.

What specifically prompted you to develop 4Pi and STED technology in partnership with Leica Microsystems?

Who took the first step to get the project rolling?

I filed a patent application for 4Pi microscopy back in 1990. In 1996, the head of development at the time, Dr. Johann Engelhardt, and the erstwhile managing director of Leica Lasertechnik in Heidelberg, Dr. Thomas Zapf, decided to acquire the rights to it and develop it in the following years. Both had the foresight to recognize that the future of optical microscopy lies beyond the diffraction limit. After all, resolution is by far the most important property of a microscope. Everything else is secondary – the purpose of a microscope is, after all, to resolve minute details. Unfortunately, that gets forgotten from time to time.

It's understandable, because there haven't been any significant breakthroughs in more than 100 years – just marginal improvements. That's why microscope development has concentrated on secondary aspects such as perfecting the illumination, enlarging the image field and improving brightness, mechanical precision, computerization and ease of use. Resolution has simply always been what it was. But different rules will apply in the future: a research microscope can feature the best possible ease of use, plenty of contrast methods, sophisticated program control and every conceivable convenience – but if it doesn't deliver maximum resolution, it's missing the point. Show a potential customer a sharper image and you won't need to deliver a long sales speech. Conversely, market demand dwindles rapidly for instruments that don't boast the best possible resolution. I expect quite a shakeup in the coming years.



“The point of any research microscope is to deliver an image with the highest possible resolution, nothing else. If it doesn’t, then it immediately loses its ‘raison d’être’.”

Have you always used Leica Microsystems instruments in your scientific work, or did that come about because of a specific project?

I wrote my doctoral thesis in the late 1980s at the University of Heidelberg, but in the offices of Heidelberg Instruments, a company that was associated with Wild Leitz GmbH at the time. Part of the company was later taken over by Wild Leitz, and that put me in direct contact with the team of the Leica predecessor. Many of them are still working for Leica Microsystems today. The close cooperation and personal trust that arose over the years isn't something one can easily replace. I stayed in touch with them even during my stint in Finland for nearly four years in the mid-1990s and after moving to Göttingen in the late 90s. I also knew that Leica was one of the very few companies with the technical expertise to take the highly academic results of my basic research work – like nanoscale optical microscopy – and apply it to instruments that can be used by anyone.

What drives you in the search for new scientific findings? Abstract scientific curiosity? Personal ambition? The will to improve the lives of your fellow humans?

First and foremost, I really enjoy what I do. That's what motivates me. I look forward to my work every morning and I'm delighted by the progress I make, be it large or small. That satisfaction that I experience every day, regardless of the significance or visibility of my successes, is a part of the quality of my life. It also steels me against failures and has kept me moving forward over the years.



Over one hundred years ago, the stated objective of Ernst Leitz was to be active 'with the user and for the user'. How do you see that – what can the industry do to support users today? And what specifically can users in the scientific community look forward to? What are the benefits they want?

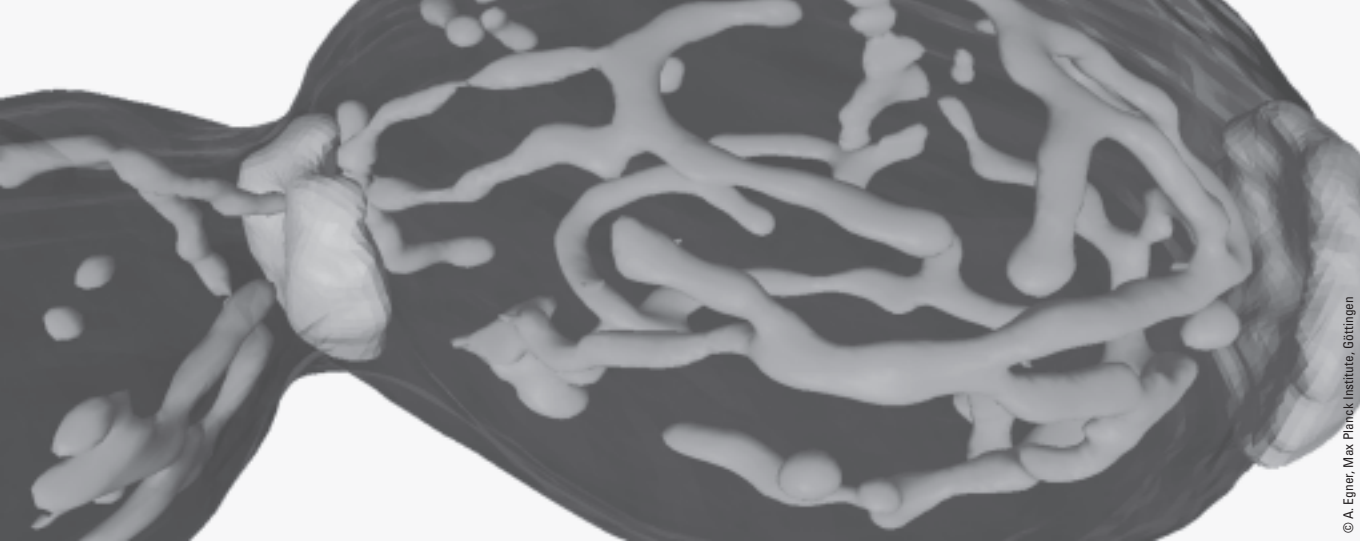
Users expect the most powerful tools possible. The most important discoveries were made with instruments that delivered maximum performance in their core functions and pushed the limits of the technically feasible. Naturally, service and maintenance support is crucial for equipment of that caliber. And it goes without saying that users expect to be kept abreast of current developments. I believe it's more important than ever before for scientists to choose suitable instruments. The right instrument at the right time can literally shed a whole new light on a question. Just choosing the proper scientific tools can in some cases render other work obsolete immediately, no matter how much diligence went into it. A company that manufactures high-tech instruments should therefore be intent on satisfying those very fundamental demands quickly and flexibly. It must provide scientists unbiased information about their performance and limits. And it must be dedicated to helping them realize the full potential of their equipment.

Pioneering – the exploration of new frontiers – is not only central to the Leica Microsystems identity, it's also a core value of your own scientific work. What does being a pioneer feel like? Tell us about the appeal of blazing trails.

Moving forward into unknown territory, making discoveries and being responsible for groundbreaking inventions are a way of attaining a bit of exclusivity – albeit for only a very short time. It lets you be the first to see where a major development – and perhaps even the stream of knowledge itself – is going. You can even affect its direction. That's certainly part of the attraction. It's exciting and satisfying at the same time. If they want, scientists have the opportunity to do their bit to influence the course of events.

Scientific pioneers often only advance by trial and error. Hypotheses frequently turn out to be dead ends. How do you deal with setbacks?

In my experience, setbacks are more useful than you might imagine. They tend to be sobering and prompt new thinking. Most of the setbacks I encountered while working on maximizing resolution ultimately moved me forward. Admittedly, it was frustrating at the time, but in the end I succeeded. Also, one should never lose sight of overall technical progress. Physical ideas that were considered complex only yesterday can now be realized on an industrial scale with relative ease. The necessary components today are far superior to those available at the time the idea was taking shape. Consider how easy it is today to generate light in any color using solid-state lasers. Or think of today's photodetectors. On average, their efficiency has tripled in the past 15 years. Or nano-positioning technology – it's faster, cheaper and more precise than ever before. And then there's the performance explosion of computers and peripheral devices – there's no end to the development in sight.



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Mitochondrial network architecture during budding, 3D-surface rendered image, Leica TCS 4PI

“It’s now possible to realize things that once were unfeasible due to simple technical limitations.”

Breaking Abbe's barrier opens whole new perspectives for the life sciences.  
What are your next projects? Where is your journey going?

While we now understand the physics of overcoming the diffraction limit, we haven't yet realized the maximum attainable resolution. Far from it. It's breathtaking to see the sharpness that we can achieve with light microscopy today. Resolutions of better than 20 nm in the focal plane of the objective have become routine in laboratory environments.

In the early 1990s, that was still inconceivable for light microscopy. And there are no serious technical or monetary issues preventing us from achieving those performance levels in commercial instruments as well. The surprising thing is that the technical preconditions are relatively undemanding. I'm convinced that in five years, virtually all good biomedical laboratories the world over will have, or at least have routine access to, fluorescent nanoscopes. Nano-resolution STED microscopy has enormous potential.



“A momentous development is currently taking shape, and many have not yet recognized its significance.”

You seem to invest all of your energy into research and working on new findings. Do you still have time for a personal life? How do you unwind? Do you have such a thing as your own personal terra incognita?

I spend as much time as possible with my family – especially my children. At the moment, the kids are into model helicopters. When I was their age, such models relied on combustion engines that were heavy, noisy and smelly, and that didn't exactly work wonders for your popularity with the neighbors. They were also quite a challenge to fly. Things have gotten much better, though – thanks to light, powerful lithium-ion batteries, electric motors have become more than adequate. They are so simple and inexpensive that you can actually fly a small helicopter in a room. The kids have a terrific time, even when the weather outside is miserable. Fifteen years ago, could you have imagined that such a complex toy would one day be so simple? It's always a good idea to give pioneering spirit the space it needs, and to never underestimate progress ...

