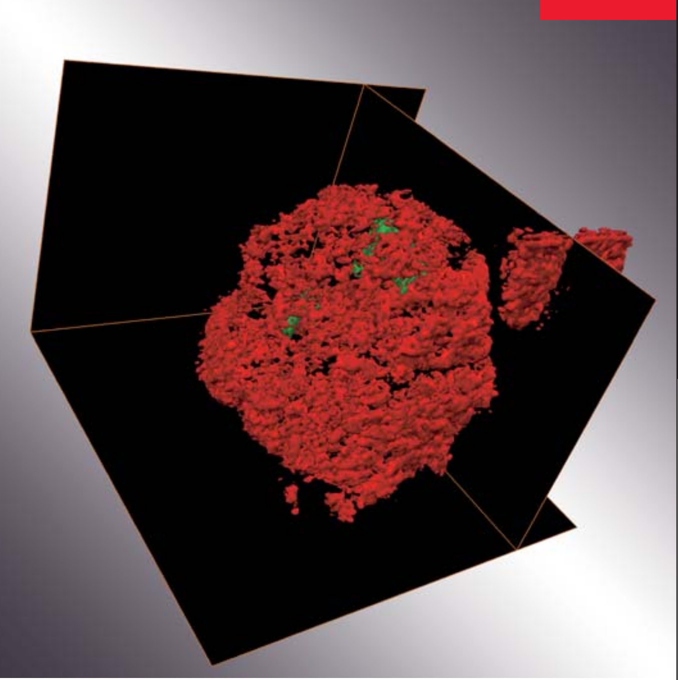

Leica Microsystems – a Tradition of Innovation

Outstanding Product Developments in High-tech Optics

Leica

MICROSYSTEMS

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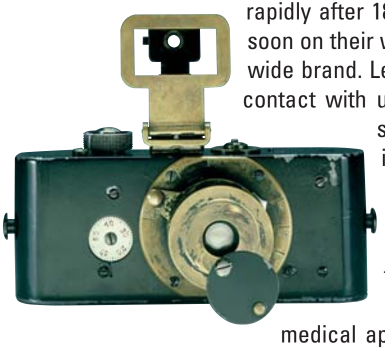
Leica Microsystems – a Tradition of Innovation

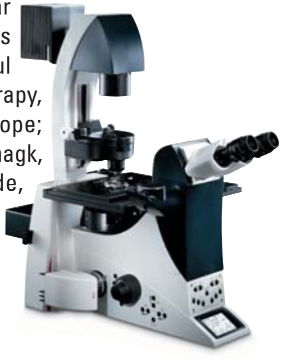
Leica Microsystems is remarkable for its record of nonstop innovations. With its pioneering developments, the international company has made technological history numerous times. Originating in the 19th century as a family-owned firm in Wetzlar, Germany, Leica Microsystems, the designer and producer of high-tech precision optic systems, now belongs to the Danaher Corporation, a US listed company. Up to the present day, the company has always remained true to the very principles that made Ernst Leitz I successful all those years ago: close cooperation with customers, participation in scientific developments and their direct implementation in future technology. This has led to the creation of outstanding products at Leitz (later renamed Leica Microsystems), such as the first full binocular microscope, the first comparison macroscope for forensic applications and the world's first fluorescence microscope.

Recently, Leica Microsystems won the coveted German Business Innovation Award–formerly known as the Innovation Award of German Industry–for the third time for milestones in optical development. In 1984, the prize was earned for the ELSAM acoustic microscope and in 2002 for the DUV objective for photomask and wafer fabrication. Just three years later, in 2005, the Innovation Award again crowned one of Leica Microsystems' product achievements: the high-end fluorescence microscope Leica TCS 4PI. For the first time, the TCS 4PI enables three-dimensional examination and imaging of structures and processes in living cells at resolutions as great as 100 nanometers.

Leitz becomes a worldwide brand

Ernst Leitz I, who took over Carl Kellner's optical institute in Wetzlar in 1869, possessed both an understanding of physics and an entrepreneurial spirit. He introduced volume production into the Wetzlar manufacturing facilities. Sales increased rapidly after 1871, and Leitz instruments were soon on their way towards becoming a world-wide brand. Leitz sought to maintain constant contact with users, and designed the microscopes with a view to the specific requirements of his customers–a principle which is a continuous thread running from the company's early days through to the present. Microscopes were produced for biomedical applications as well as industrial analysis, such as mineralogy. By 1880, the company had already reached an annual production of 500 instruments. It shipped its 10,000th microscope in 1887, the 20,000th four years later, and reached the 50,000 mark as early as 1899. Bacteriologist Robert Koch received the company's 100,000th microscope in 1907–the beginning of a tradition intended to create a strong bond between the Wetzlar factories and famous researchers and Nobel Prize winners. Paul Ehrlich, the founder of chemotherapy, received the 150,000th microscope; Nobel Prize winner Gerhard Domagk, who discovered sulfonamide, received number 400,000.





Ernst Leitz becomes Leica Microsystems

In the beginning of the 1970s, Leitz formed a cooperation with the Swiss optics company Wild Heerbrugg, which led to the founding of the Wild Leitz Corporation in 1986.

Just a few years later, in 1990, another merger took place with the Cambridge Instruments Group, which itself had already united several companies with rich traditions. In addition to Cambridge Instruments, these companies included the Heidelberg-based microtome manufacturer, Jung, the Vienna-based optics manufacturer, Reichert, and the entire microscopy area of the North American optics companies Bausch & Lomb and American Optical, and thus the entire North American microscope industry.

Bausch & Lomb traces its history back to Charles Spencer, who brought his first microscopes to the market as early as 1846. In the late 1990s, Leica Group spawned three independent optics companies: Leica Microsystems, Leica Camera and Leica Geosystems. In July 2005, after about seven years of ownership by the investment firm LM Investments S.à r.l., Leica Microsystems was bought by the US-based Danaher Corporation, which is listed on the New York Stock Exchange.

Leica Microsystems – a global company

Today, with eight manufacturing facilities in six countries, sales and service organizations in 19 countries, sales partners in over 100 countries and approximately 3300 employees,

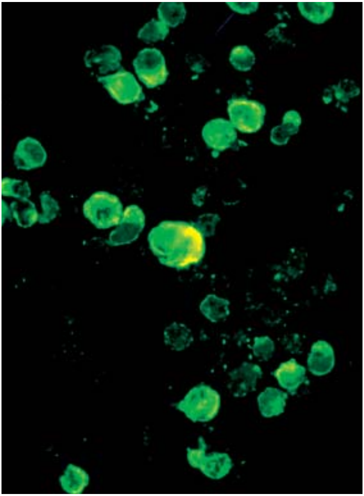
Leica Microsystems is an international technology group that has never lost touch with its deeply rooted traditional product lines. Despite the wide variety of its products, locations and business units, light microscopy remains a primary focus for the company and provides the foundation for many other activities. Examinations with light microscopes, such as those manufactured in Wetzlar, Singapore or Shanghai, are the starting point for discovering the secrets of the microcosm–not only in schools and universities, but also in clinical laboratories and industrial and biomedical research institutions.

Milestones of optics

The path for microscope development was cleared by the successful synthesis of microscopy and photography. For example, the development of the legendary Leica small image camera by Oskar Barnack was a pioneering step in the history of technology.

In 1913, the Ernst Leitz company presented a first full-featured binocular microscope. The first polarizing microscope followed in 1925.

The first comparison macroscope for forensics was produced in 1931, a spectacular application of modern technology to obtain criminological evidence.



In 1932, the company introduced incident light fluorescence to the market; three years later, it introduced the photometer, developed by Max Berek.

The postwar era continued this tradition, but the focus of change turned to electronics–computing technology began aiding microscope optics as early as 1953.

The first fluorescence microscope and Green Fluorescent Proteins

Fluorescence microscopy has a long tradition at Leica. In 1911, Vienna-based Reichert, which today belongs to Leica Microsystems, was the world's first company to develop a fluorescence microscope–a technique which has since become an invaluable part of biomedical research. A fluorescent material is genetically fused to an enzyme to be examined. This visualizes the intracellular phenom-ena, which are usually invisible to the human eye. A breakthrough in cell biology is the successful imaging of the smallest cell structures using "Green Fluorescent Proteins," abbreviated as GFP, CFP, YFP, RFP etc.

The DNA of GFP, which was discovered in a green fluorescent jellyfish in 1994, is fused to gene sequences and introduced to the cell. This results in a fluorescent protein that survives the conversion process from the DNA to the amino acid to the functionally folded protein without any damage. It fluoresces and allows active processes in the living cell to be observed.

Hearing what no one can see:
acoustic microscope receives reflecting sound

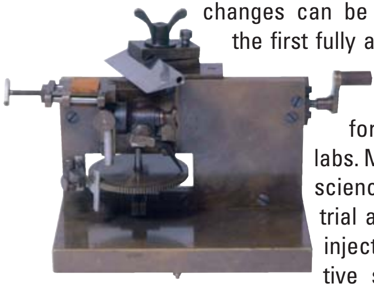
Bats use ultrasound waves in the frequency range of ten to 120 kilohertz to orient themselves in their environment. They transmit short impulses and receive the sound as it reflects off obstacles. This is how they detect their prey as well as objects in the way of their flight path. For the world's first volume-produced ultrasound microscopes, the "prey" is defects in materials. Specifically, these microscopes find defects that are invisible to the naked eye but are "heard" by the acoustic microscope, which, in turn, makes them visible to the eye.

This microscope, which received the German Business Innovation Award in 1984, works with a system just like the bat's. However, the frequency range is much greater, spanning from ten megahertz to two gigahertz.

The acoustic objective of the Ernst Leitz Scanning Acoustic Microscope (ELSAM) generates and transmits sound impulses and receives their reflected echoes. The echoes are then converted into video signals and appear on a monitor in the form of pixels.

From diagnostics to treatment

In clinical diagnostics, a tissue sample is prepared in multiple sections before the histologist or pathologist observes them under a microscope. Using microtomes and cryostats, for example, thin sections of biological tissue are created and then colored with special stains so that benign or malignant tissue changes can be detected. Leica introduced the first fully automated staining station to the market in 2003, an intelligent and flexible solution for cytology and pathology labs. Microtomy is not limited to life sciences, but is also used in industrial areas to cut plastics, foils or injection-molded parts, automotive sheet metal, leather, foods and many other products.

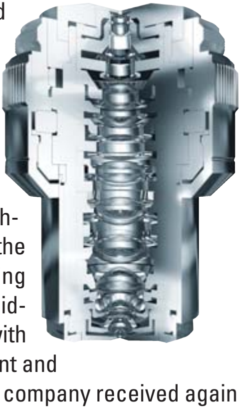


In the manufacture of ultrathin sections for electron microscopy, Leica draws on decades of experience in Vienna. There, Professor Hellmut Sitte developed one of the first ultra-microtomes in the 1950's, which Leica has continued to produce ever since. Today, the Vienna business unit remains the world's market leader in specimen preparation for transmission electron microscopy.

Leica surgical microscopes likewise have set standards and can be used in a wide variety of applications. Surgical microscopes from Leica Microsystems are used directly on the patient, primarily in neurosurgery and ophthalmology.

Making the impossible possible: a microscope objective with an unlimited service life

Wafer and photomask testing continuously places increasing demands on the optical resolution of the objectives. The miniaturized structures on wafers and chips can only be imaged using deep ultraviolet light at a wavelength of 248 nanometers or less. However, the cement used between the individual lenses of common objectives only withstands the ultraviolet light for a limited time. It quickly darkens, and the expensive objective suddenly has to be replaced with a new one. In 2001, Leica Microsystems developed a high-resolution microscope objective for the semiconductor industry, thus making possible what the industry had considered impossible. The DUV objective with "airspace technology" needs no cement and thus has an unlimited service life. The company received again the German Business Innovation Award in 2002 in the category of medium-sized companies for this revolutionary

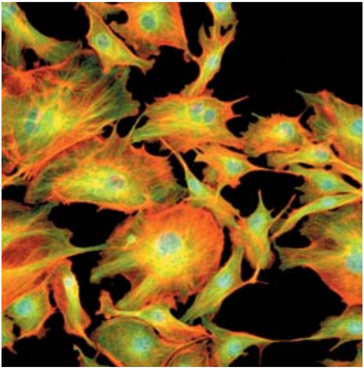


microscope objective.

The following year, Leica Microsystems enjoyed market success with digital microscopes for biomedical research and applications in industry.

Living cell image analysis and processing

As early as 1967, image analysis had its premiere at Leica Microsystems–a new level of quality in the process of visualizing microscopic structures. This method provides quick and accurate quantitative analysis of an image. Image information is localized and converted into a digital form for processing and analysis. Today, the company develops state-of-the-art image-analysis systems. These are used, for example, in cytogenetic research to locate the genes responsible for hereditary diseases. Cutting-edge image-analysis systems help to increase the efficiency of cancer treatment. The latest development in the area of image analysis and processing allows living cells to be imaged in a way that is both quick and nonin-vasive.

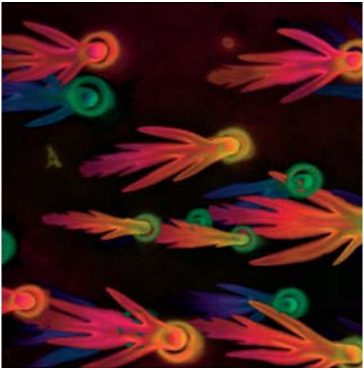


Leica high-end products of the future have one thing in common: the Leica Application Suite, in short LAS. This software offers a uniform user interface with consistent, easy-to-use functions for specific, highly complex applications. In these times, as the importance of electronics and software continues to grow for microscopy, a homogenous software and application landscape is a crucial advantage for the user.

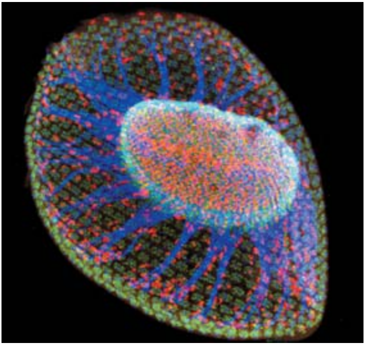
Tiny structures in three dimensions – confocal laser scanning microscopy

Examination with light microscopy does not always make it possible to gather all information from a specimen. Egyptian papyri, for example, have often become illegible due to their poor state of preservation. Even using stereomicroscopes, experts cannot always decipher the texts–written in ink thousands of years ago–with certainty. Confocal laser scanning microscopy allows the meaning of the texts to be accessed again. Freely translated, "confocal" means viewed "with the focus," so that only the optically sharp focal plane can be seen.

Confocal technology eliminates all out-of-focus image information from other focal planes. The thinner the focal plane, the sharper the images will be. The object being examined is scanned by a light spot and optically cut into thin sections. Three-dimensional reconstructions can then be calculated from these sections.



The result is an image with high depth of sharpness that can be rotated, viewed and measured from all sides in the computer. Going back to the papyrus example, optical sections can be made of difficult-to-read areas, which then–as in computer tomography–are used for a three-dimensional reconstruction. Even if no more ink remains on the papyrus, the impressions of the stylus can be detected. Lower or higher structures, for which only blurry images or none at all could be provided previously, suddenly become clear.



Confocal systems of the future

Primarily, however, confocal microscopy has been established as fluorescence microscopy in life sciences, particularly in basic research, where ever-increasing resolution leads to new

insights. Today, Leica Microsystems continues to advance the development of the confocal microscope, which fifteen years ago was a spectacular, but fragile and service-intensive high-tech system. What was once a rare instrument has since become a standard, and the latest version, the Leica TCS SP5, sets new standards as a broadband confocal system. In addition, the new dynamic acousto-optical beam splitter (AOBS) supports multi-spectral imaging for specimens with multiple stains. This Leica development also made it to the final round of the German Innovation Award!

However, the current peak of innovation is the TCS 4PI, a high-tech fluorescence microscope that, for the first time, allows cells to be imaged at resolutions as great as 100 nanometers. This new microscopy method, which was discovered by Professor Stefan Hell, Director of the Max Planck Institute for Biophysical Chemistry, and developed for real-world use by Leica

Microsystems, makes it possible to study the tiniest intracellular details in living cells. In basic research, it opens new doors for developing effective medications to treat many diseases.

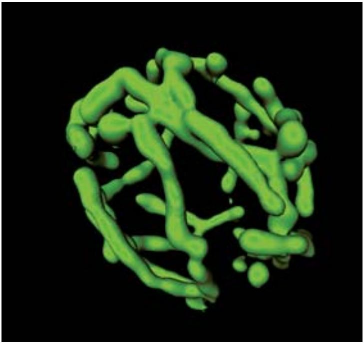
The reward: Leica Microsystems' third German Business Innovation Award for 2005!

Getting closer to the building blocks of life

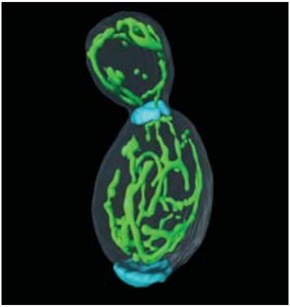
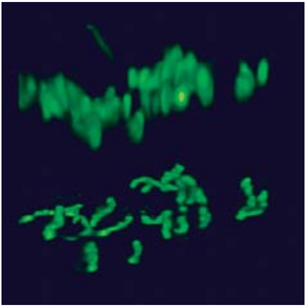
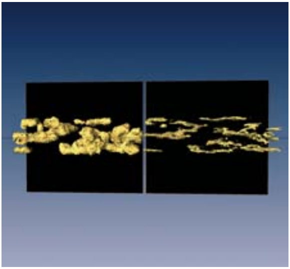
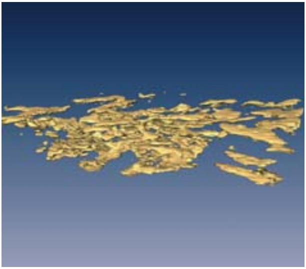
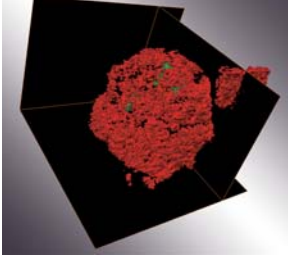
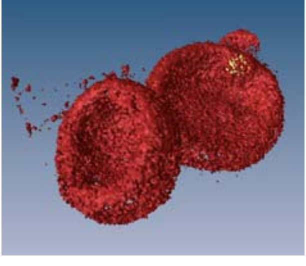
Due to the wave structure of light, an objective cannot concentrate light into a point, but only into a beam spot. The smaller the beam spot is, the higher the resolution. Therefore, the task of an objective is to make the illumination of the specimen more efficient. In doing so, the incident two-dimensional light wave is converted into a three-dimensional spherical wave that hits the focal point. However, this spherical wave is not completely round like a ball, and thus the light spot has an oval shape. The consequence is that 3D structures, particularly those along the optical axis, cannot be separated so well and thus are distorted.

4Pi: The full solid angle of a real spherical wave

The 4Pi microscope uses two opposing objectives to create a nearly complete spherical wave using interference. This principle gives the microscope its name, "4PI"–a reference to the full solid angle of a real spherical wave. When applied to the excitation light in fluorescence microscopy, this leads to a 3 to 7 times narrower focus along the microscope axis.



The new 4Pi technology allows spatial imaging of microscopic structures with a sharpness of detail and increase of structural information that have never before been possible with any other commercial light microscope in the world. Thanks to this additional information, scientists have been able to gain broader and deeper understanding of processes in living cells and cell organelles and to reach new insights about structures and their interactions. The Leica TCS 4PI, the winner of the 2005 Innovation Award, allows enormous progress to be made in the development of medications for treating protein-based diseases such as Alzheimer's, diabetes and malaria.

Combining innovation and tradition

"With the user, for the user." The philosophy of Ernst Leitz I remains the guiding principle of Leica Microsystems' successful innovations to the present day.

Leica offers its customers perfectly tailored solutions for three-dimensional visualization, measurement, analysis and imaging of the smallest structures. The fact that Leica has received the Innovation Award three times, and was a finalist once, confirms its technological leadership. That users of Leica systems, in turn, make pioneering achievements in their own fields of research and garner scientific laurels confirms its sophisticated and systematic innovation process: all development begins and ends with the customer.

Thanks to intensive dialog with users at universities and other research institutions, Leica can immediately translate scientific developments into future technologies. Thus, the principle that was applied by pioneers Carl Kellner and Ernst Leitz as the starting point for the quality of their instruments is still practiced today.

Winner 2005

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