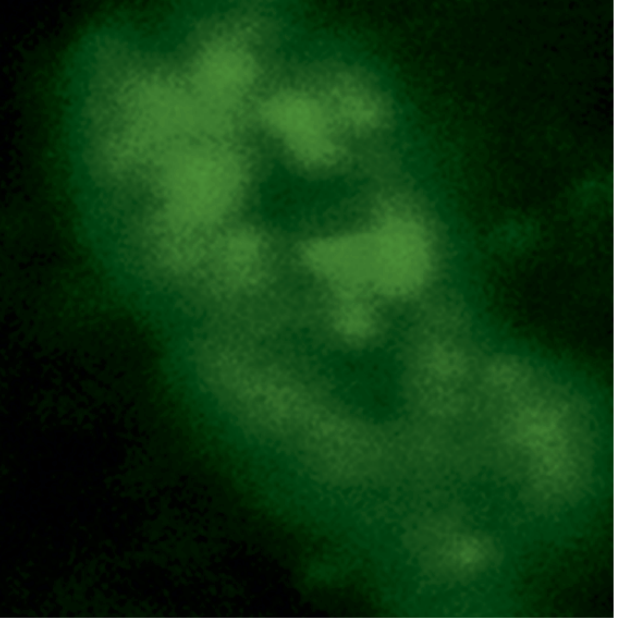
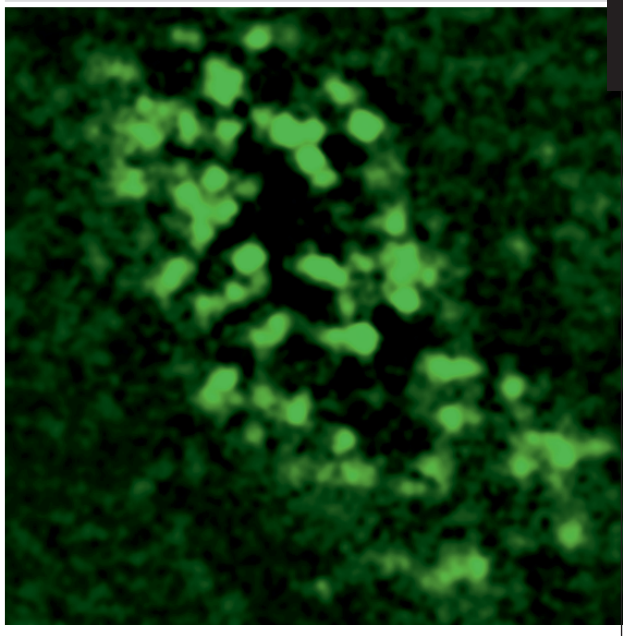


Liprin distribution in the neuronal active zone of a *Drosophila* larvae. Confocal image

Same sample imaged with STED



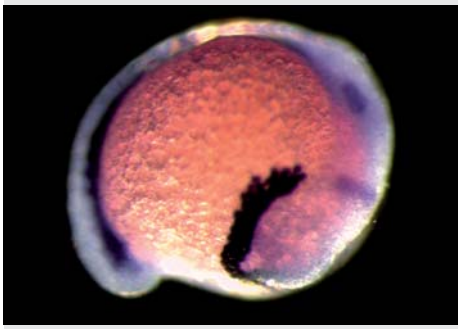
Leica High Resolution and Superresolution Microscopy

Leica Microsystems leads the product innovation in High Resolution and Superresolution Microscopy

Leica
MICROSYSTEMS

Modern microscopy for life science research, demands imaging resolution up to and beyond the 200 nm Abbe barrier. To see life in context at the sub cellular level, novel imaging methods are required. Only then can we see the full spectrum of life.

Leica Microsystems meets this demand with an ensemble of exciting new instruments and technologies in widefield, stereo and confocal microscopy.



Zebrafish larva

FusionOptics™

FusionOptics™ in Stereo Microscopy

Stereomicroscopes, often referred to as dissecting microscopes, have been used to image microstructures for decades whilst manipulating, sorting, polishing or cutting the specimen. In the past, stereomicroscope users had to choose between higher image detail and better 3D depth perception, as these factors are inversely proportional to each other.

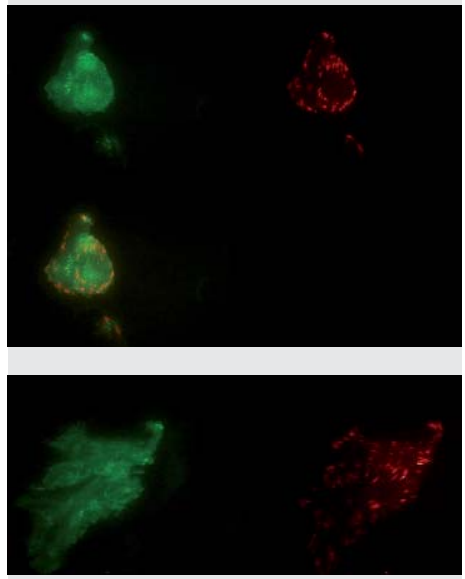
Such a sacrifice is no longer necessary due to the new FusionOptics™. Their design provides a high-resolution image to one eye and a high depth image to the other eye. These images are automatically fused by the visual cortex, which results in stunning image detail and huge depth relief. This design is employed in the brand new Leica M205 C stereomicroscope, which provides easy positioning of tools and manipulators in 3D with unprecedented resolution. The Leica M205 C is the world's first stereomicroscope with a fully apochromatically corrected 20.5:1 zoom. In the zoom range from 0.78x to 16x, the resolution increases continuously up to 1050 lp/mm. For the Life Science Researcher, the benefit is an easier, more comfortable to use tool, offering both versatility and brilliant images.

TIRFM

TIRF Microscopy System

A major gateway has been opened in widefield microscopy of living cells with the advent of **T**otal **I**nternal **R**eflection **F**luorescence **M**icroscopy (**TIRFM**). This is a highly sensitive technique that gives a high signal-to-noise ratio and z-resolution of approx. 100 – 300 nm. For example, it allows the visualization and analysis of vesicle transport and signalling events, as well as kinetic studies and single molecule detection.

In order to offer this technique to a wide community of researchers, Leica has developed the first fully automated TIRF system; the Leica AM TIRF MC. At the heart of the system lies a dedicated scanner, which enables precise control of the penetration depth of the evanescent wavefield. LAS AF software provides automated alignment for the highest quality images and makes data collection easy. Equipped with up to four solid-state lasers with wavelengths of 405 nm, 488 nm, 561 nm and 635 nm, the system allows excitation of all the important fluorochromes. Even during fast wavelength switching, the TIRF penetration depth is maintained, allowing the TIRF imaging method to be combined with FRET experiments. All optical TIRF components are optimised for the highest transmission, giving the ultimate in TIRF imaging quality, speed and brilliance. High-speed acquisition of up to 30 frames per second with simultaneous wavelength changing makes the Leica AM TIRF MC an ideal tool for advanced live cell studies.



Breast carcinoma cells.
Green: Rab-8 GFP, red: Paxillin RFP

STED

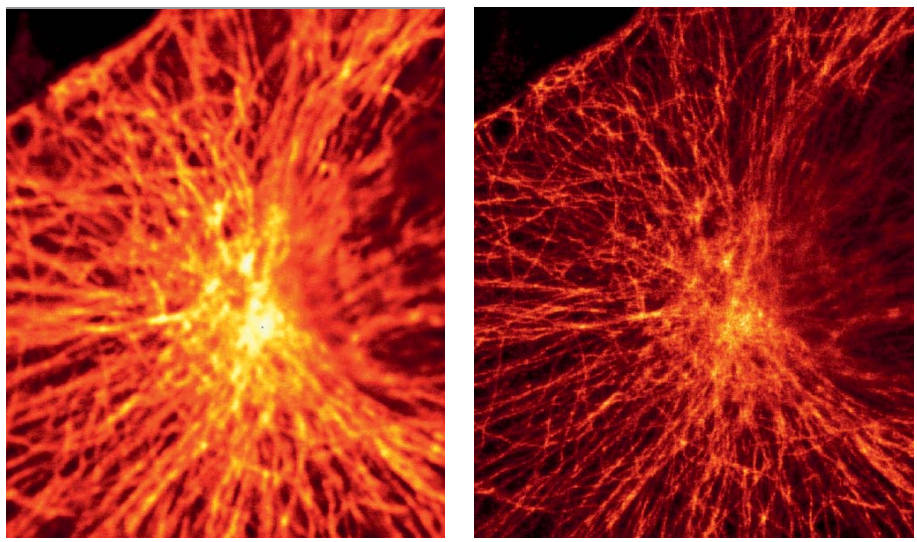
STED Superresolution Confocal/Multiphoton System

When it comes to breaking the 200 nm resolution barrier, Leica Microsystems leads the way! A new groundbreaking technology: **S**timulated **E**mission **D**epletion **M**icroscopy, (**STED**) is available today with the Leica TCS STED. The Leica TCS STED microscope illuminates the sample via two tightly synchronized pulsed laser beams. The 635 nm wavelength excites the fluorochromes of the sample the same way a conventional confocal system does. The excitation laser pulses are directly followed by a ring shaped illumination of a Ti:Sapphire Infrared laser. This pulse inhibits the fluorescence in the outer regions of the illuminated spot, resulting in a superresolution spot which is scanned across the sample.

This novel concept was integrated into the versatile confocal and multiphoton platform Leica TCS SP5 to facilitate break through research in neuroscience, membrane biology and genetics. Cancer research, life-style related and degenerative disease research will benefit strongly from this technology.

Any Leica TCS SP5 confocal microscope can be upgraded to STED.

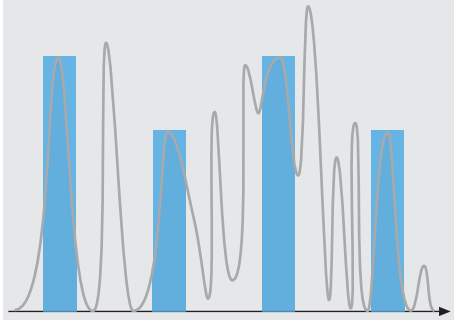
Operation is made easy by auto-alignment of the STED beams and quick and easy switching between STED and confocal mode at the touch of a button.



Microtubular network in Vero cells, Left: confocal; right: STED

RESOLFT

Based on the saturation of reversible single photon optical transitions in molecules, RESOLFT microscopy has the potential to provide resolution of tens of nanometres non-invasively in 3D structures. In preparation for the future, Leica has licensed general RESOLFT technologies.

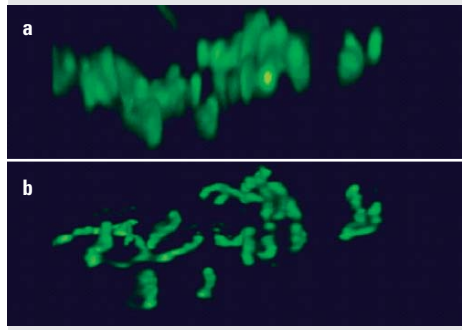


4Pi

4Pi Microscopy

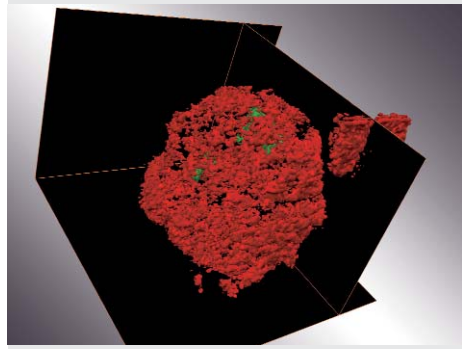
With the first commercially available superresolution microscope, the Leica TCS 4PI, the object of investigation is imaged by two high-quality objectives arranged opposite each other. Applied to fluorescence microscopy, this leads to a 3 to 7 times sharper focus along the microscope axis.

The result is an axial resolution of around 100 nanometers and an almost isotropic focal spot, ideal for 3D reconstructions with resolution beyond Abbe's limit. Key applications of the Leica TCS 4PI exist in a wide range of structural cell biology investigations and in the research of infectious diseases.



a Confocal
Live yeast cell – mitochondrial protein distribution, Label: GFP, Objective: 63x1.2 W

b STED
Courtesy of Jörg Bewersdorf, MPI for Biophysical Chemistry, Göttingen



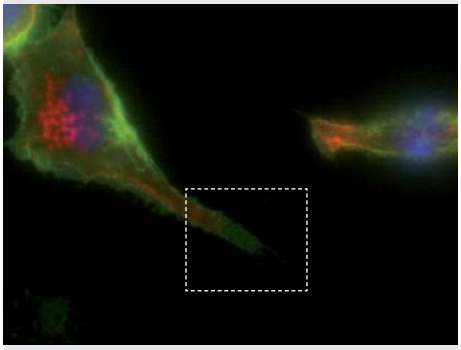
Malaria infected human red blood cell
Courtesy of J. Dvorak & F. Tokumasu, NIH, Washington, USA

AFM

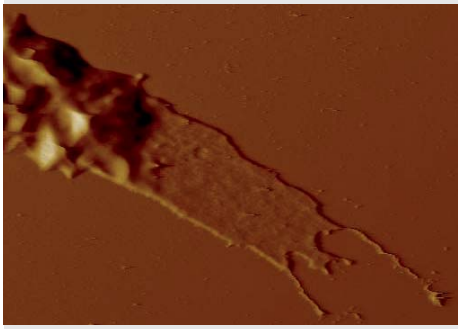
Combining Atomic Force and Light Microscopy

In considering purely optical methods, co-operation between Veeco and Leica Microsystems reveals a powerful combination between **A**tomic **F**orce **M**icroscopy (**AFM**) and optical microscopy:
by close collaboration, a system has been developed which allows the study of biological structures and dynamic processes *in situ*. Clear benefits of AFM and optical microscopy are seen for Life Science applications. Structures identified with optical microscopy can be further investigated by the application of high-resolution AFM-imaging. The direct correlation between fluorescence and sample topography on the nanometer, allows insight into structural details not previously visible. It is now possible to select and pre-screen the region of interest optically and perform nanomechanical measurements for elasticity, molecular unfolding and more. Force measurements at the molecular and cellular level, e. g. for studying receptor ligand binding events using functionalized tips, open even further research possibilities. For more information visit please visit:

www.veeco.com/info/bioscopeII
www.leica-microsystems.com/afm



Mouse peritoneal macrophages. Fluorescence.
Red: actin, green: nucleus, blue: membrane



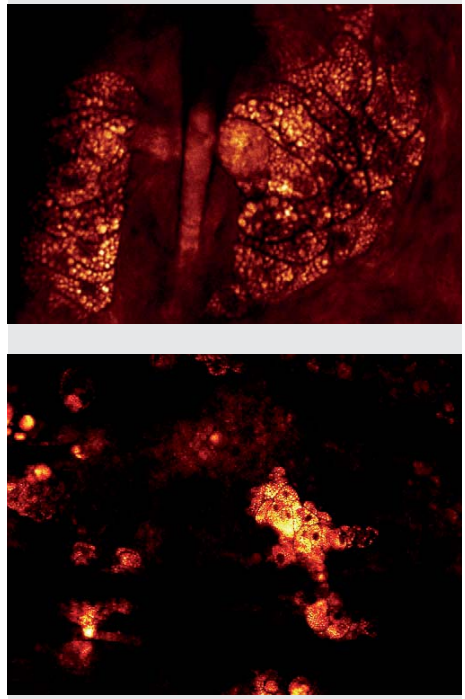
White box indicates area scanned with Veeco BioScope™ II AFM
Courtesy of Peter Hanley,
Institute of Physiology II,
University of Muenster, Germany

CARS

CARS Microscopy

Coherent **A**ntistokes **R**aman **S**cattering (**CARS**) microscopy allows rapid and non-perturbative imaging of biological specimen with chemical selectivity. No specific staining is required. Visualization in CARS microscopy arises from the intrinsic vibrations of molecules only.

The technology was developed in the lab of Xiaoliang Sunney Xie, Professor of Chemistry and Chemical Biology at Harvard University. Leica Microsystems and Harvard University's Office of Technology Development (OTD) recently announced a license agreement to develop CARS microscopy as an extension of confocal/multiphoton microscopes. A corresponding commercial product is planned.



Courtesy of Sunney Xie, Department of Chemistry and Chemical Biology, Harvard University, Cambridge MA, USA

All in all

Leica Microsystems presents an outstanding range of tools to meet today's exciting challenges in research –

- For the highest resolution in **Stereo Microscopy**
- in **TIRF** widefield imaging, or
- in resolving structures smaller than 100 nm with **STED** and **4PI**,
- as well as combining mechanical measurements and manipulations with optical surveillance using **AFM**.

These products ensure that Leica Microsystems is at the fore front of cutting edge microscopy and your first choice partner for innovation and excellence in research. All our featured solutions share a common intuitive graphical user interface, offering easy operation and fast training of users.

Leica Microsystems – the brand for outstanding products

Leica Microsystems operates internationally in four divisions, where we rank with the market leaders.

• Life Science Research Division

Leica Microsystems' Life Science Research Division supports the imaging needs of the scientific community with advanced innovation and technical expertise for the visualization, measurement and analysis of microstructures. Our strong focus on understanding scientific applications puts Leica Microsystems' customers at the leading edge of science.

• Industry Division

The Leica Microsystems Industry Division's focus is to support customers' pursuit of the highest quality end result by providing the best and most innovative imaging systems for their needs to see, measure and analyze the microstructures in routine and research industrial applications, in materials science and quality control, in forensic science investigations, and educational applications.

• Biosystems Division

The Biosystems Division of Leica Microsystems brings histopathology labs and researchers the highest-quality, most comprehensive product range. From patient to pathologist, the range includes the ideal product for each histology step and high-productivity workflow solutions for the entire lab. With complete histology systems featuring innovative automation and Novocastra™ reagents, the Biosystems Division creates better patient care through rapid turnaround, diagnostic confidence and close customer collaboration.

• Surgical Division

The Leica Microsystems Surgical Division's focus is to partner with and support micro-surgeons and their care of patients with the highest-quality, most innovative surgical microscope technology today and into the future.

Leica Microsystems' mission is to be the world's first-choice provider of innovative solutions to our customers' needs for vision, measurement and analysis of micro-structures.

Leica, the leading brand for microscopes and scientific instruments, developed from five brand names, all with a long tradition: Wild, Leitz, Reichert, Jung and Cambridge Instruments. Yet Leica symbolizes innovation as well as tradition.

Leica Microsystems – an international company with a strong network of customer services

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