FEI COMPANY™
TOOLS FOR NANOTECH

The vision of life sciences at the nanoscale

Exploring living systems at the molecular level

Look into the future of biodiscovery

The nanorevolution isn't about technology – although the science of the very small (<100 nm) promises to be the most profoundly transforming technology of our era. It's simply the realization that life is ultimately controlled by forces and processes operating at the scale of atoms and molecules.

At some point, you'll want to see what you're looking at

The more we learn about biological systems, the more we begin to appreciate their vast complexity. Cells, quite literally, are 'nano-factories'. And understanding the operation of the machines in these factories requires intimate knowledge of the relationships between form, function and location, from cellular down to atomic scale. Despite tremendous advances in analytical techniques for identifying and characterizing biomolecules and their interactions, life scientists are still 'feeling their way' through complex research using traditional methods. As one proteomics researcher wryly put it, "I spend most of my time trying to think like a protein." But the real proof of discovery is in the subtle details – and sometimes a single picture is worth a million datapoints. We make those pictures possible.

Exploring nature at the nanoscale

Today, using powerful transmission and scanning electron microscopy from FEI, it is routinely possible to see and study living systems down to the level of individual molecules. To explore, in vivo, the molecular mechanisms of disease, to unambiguously determine the conformation of flexible protein structures and to observe individual viruses and proteins in their natural biological context.

FEI, pioneering the path of nanodiscovery

Since 1949, FEI's electron and ion beam technologies have been helping researchers give life to big ideas at the smallest scales. Our Tools for Nanotech™ include the industry's broadest range of imaging solutions - versatile, powerful instruments that allow researchers and developers in life science, materials science and semiconductors to visualize, analyze and manipulate materials at the atomic level. But we offer more than just tools to our customers, where as scientific partners, we have a mutual interest in their success. Collaboration on projects is key for us as we support our customers working at the fore front of science.

The global imaging technology leader in NanoResearch and NanoElectronics, FEI also has a long rich history in life sciences-helping research institutes unravel the complexities of biological structure and function, and helping pharmaceutical companies develop the next generation of life-saving therapeutics. Our new NanoBiology organization takes this commitment a step further, bringing a dedicated, committed team to the nanoscale exploration of life.

Index

Take an eye-opening trip through today's world of nanobiology

FEI's pioneering work in imaging the basic building blocks of life is paying off with major breakthroughs in NanoBiology - from the rapid characterizations of proteins, cells, viruses and DNA, to the development of smarter drugs and delivery systems, to ambitious plans for developing *in vivo* devices for fighting life-threatening diseases. This brochure will give you a closer look at some of the exciting new application areas in which our products, services and scientific collaboration are playing a major role.

Structural biology - examining proteins at the molecular level

Unlike nuclear magnetic resonance (NMR) and X-ray diffraction (XRD), cryo tomography examines one protein complex at a time, enabling you to observe structural differences between individual protein complexes. Able to resolve the tertiary and quaternary structure, protein complexes and cellular structures, this novel technology bridges the gap between the atomic resolution of NMR and XRD and the sub-micrometer scale of light microscopy.

Structure of the Dictyostelium Nuclear Pore Complex by means of cryo-electron tomography, three dimensional classification and averaging.

Image courtesy of:
Martin Beck, Friedrich Förster, Mary Ecke, Jürgen M. Plitzko, Frauke Melchior, Günther Gerisch, Wolfgang Baumeister and Ohad Medalia, Max-Planck-Institute of Biochemistry, Martinsried, Germany. We gratefully acknowledge help with the design and visualization by Julio Ortiz. Details published in Science 306:1387-1390, 2004.

The full range of uses of this versatile technique are only beginning to be explored, but some typical application examples include:

- Studying membrane proteins in their natural context within the cell membrane
- Dynamically characterizing flexible, full-length proteins
- Localizing and studying proteins in different cell compartments
- Visualizing therapeutic antibodies in-situ
- Making molecular level comparisons between cell assays, animal models and human tissue

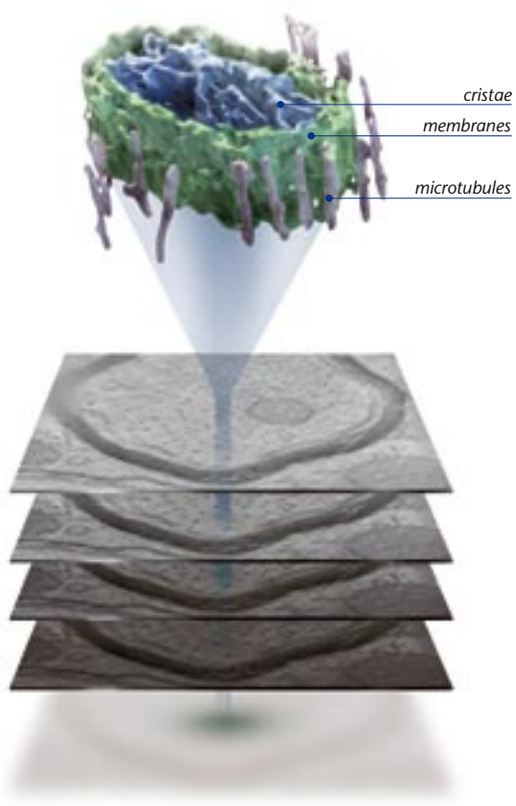
FEI's cryo tomography system consists of an ultra-high resolution TEM, such as the Tecnai™ G² Series that is equipped with Xplore3D™ imaging software.

The Tecnai G² Polara

The Tecnai G² Polara is the culmination of more than 25 years of vacuum technology development and electron optical techniques that are required for structural biology investigations. The powerful combination of advanced TEM imaging with automatic acquisition of high quality tomographic data sets enables three-dimensional understading of structures down to the atomic level. The system is a complete and intelligent 3D imaging solution for data collection, reconstruction, visualization and analysis.

Cellular tomography - mapping the inside of a cell - in three dimensions

Because most proteins function in coordination or dependence with other proteins, the knowledge of a cell's three-dimensional structure is essential to understand protein function in a living system. Cellular tomography is the only available technology that can do this. It uses advanced TEM techniques to generate an accurate, three-dimensional map of the interior organization of the cell, enabling you to analyze molecular structures in relation to the cellular architecture, the cytoskeleton and the cell organelles.



Localization of ferritin in degenerating neurons. Although it had been concluded from previous studies using light microscopy that ferritin molecules localize in the interior of the axon in degenerating nerve cells, cellular tomography exploration demonstrates that it is actually located in oligodendrocyte cells that invade the milieu of the degenerating axons-revealing a completely different mechanism for neuronal degeneration.

The image shows 3D rendering of a mitochondrion from a mouse neuron. Tomograms obtained from thick mouse brain sections were selectively segmented to highlight the mitochondrial membranes (in green), cristae (in blue) and surrounding neurofilaments and microtubules (in grey). Image courtesy of Dr. Sriram Subramaniam at the National Institute of Health, MD, USA.

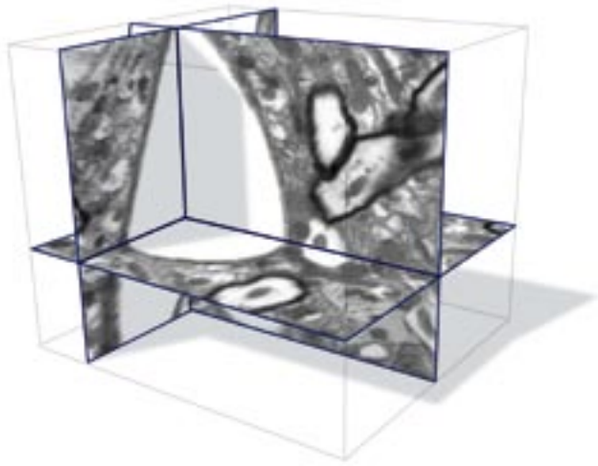
To understand how cells can interact in their natural context, it is important to understand how they are organized in a three-dimensional network. FEI's DualBeam™ automated tissue imaging offers the only clear picture of three-dimensional cellular interactions in larger tissue structures.

Automated 3D tissue imaging - seeing how cells are organized

The DualBeam electron microscope and a novel, automated *Slice* and *View*™ technique offers today's most exciting and effective method for studying the 3D architecture of tissue, whole cells and sub-cellular structures.

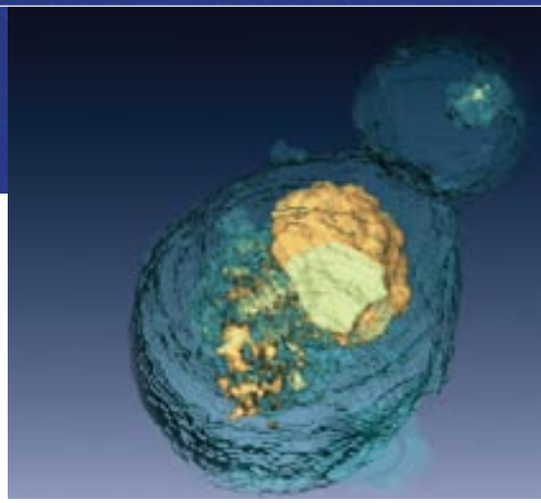
FEI's DualBeam microscope combines a Scanning Electron Microscope (SEM) with a Focused Ion Beam (FIB) in a single, fully-integrated system. The FIB acts as a 'nano-scalpel', enabling high precision cutting and slicing into samples to reveal their 3D internal structures. The SEM provides high resolution imaging of the freshly cut surfaces. Repeatedly cutting and imaging (*Slice* and *View*) yields a dataset that replicates the 3D reconstruction of the material from tissue level down to cell and organelle level.

The FIB nano-scalpel can also be used to swiftly and easily produce Transmission Electron Microscope (TEM) samples without the compression and knife-mark artifacts common to mechanical sample preparation techniques.



This image shows a 3D representation of more than 200 recorded slices using the fully automated *Slice* and *View* process of an embedded and stained section of mouse brain. The sectioned area of the sample is 13 x 13 x 8 µm and is courtesy of Dr. Graham Knott, Département de Biologie, Cellulaire et de Morphologie, Faculté de Biologie et Médecine, Université de Lausanne, Switzerland.

Cell biology - examining cellular components in their natural environment



3D rendering of a budding yeast cell using 'Slice and View'. Image courtesy of Dr. Sriram Subramaniam at the National Institute of Health, MD, USA.

Dehydrating a cell to study it can significantly alter the results of the investigation. High resolution microscopy using FEI instruments allows unique imaging of cell membrane structures in fully hydrated conditions. For examination of sub-cellular morphology in fully hydrated conditions, samples can be quickly fixed by a cryo sample preparation unit. Automated cryo-fracture techniques allow further study of interior cellular structures.

Nova NanoLab™

Nova NanoLab is a versatile, high-performance DualBeam (FIB/SEM) designed to support the high-end life science lab. The easy-to-use DualBeam software enables researchers to conceive and implement complex tasks quickly, including high resolution investigation of the architecture of whole cells in larger tissue samples.

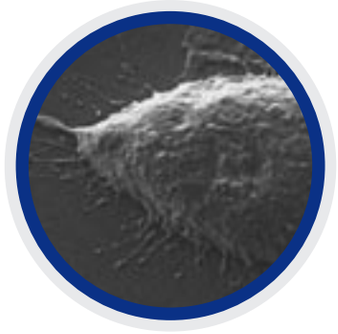


Image of fully hydrated vero cell. Courtesy of Professor Barbarisi, University of Naples, Italy.

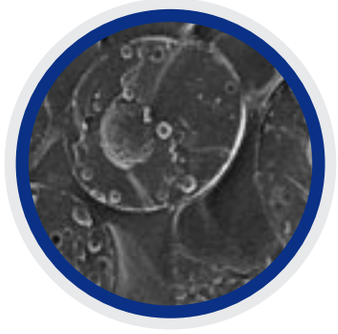
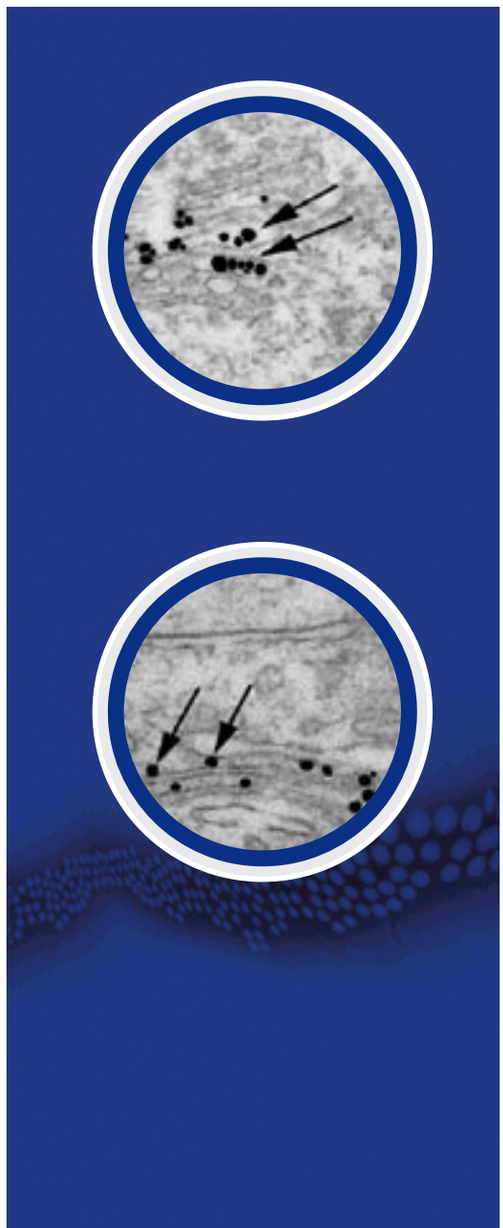


Image of cryo-fixed and fractured yeast cells. Courtesy of Dr. George McKerr, University of Ulster, Department of ABS, Northern Ireland.

Many proteins and interactions between them have been studied using biochemical means and techniques such as fluorescence microscopy and confocal microscopy. While these approaches provide a global localization within tissues and cells, electron microscopy offers a more powerful tool to examine the ultrastructural level. The use of gold labeled antibodies enables proteins to be localized with nanometer scale accuracy, and can validate whether the proposed function of the protein is realistic in the context of the organelle where the protein is found.

Protein localization - quickly locating proteins within the cell



Localization of MGP-160 protein. Immunogold nanoparticles localize the Golgi marker protein MGP-160 within the lumen. Courtesy of Aurion, The Netherlands.

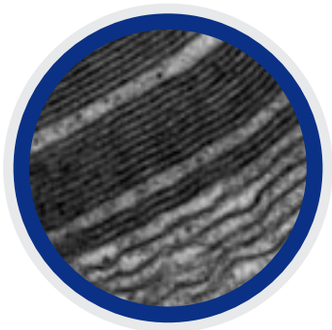
Localization of Huntingtin-related protein. Huntingtin-related protein on the outer surface of the Golgi membrane. Courtesy of Aurion, The Netherlands.

Pathology and toxicology - diagnosing ultrastructural changes

The increasing knowledge about the molecular machinery within cells allows researchers and clinicians to understand and diagnose pathological and toxicological effects in greater detail than ever before. Modern electron microscope technology enables early stage diagnosis of structural changes at the ultrastructural level. Especially in those cases where no standard diagnostic tests are available, electron microscopy provides a powerful and easy-to-use tool to reveal the underlying causes of disease.

The Tecnai™ G² Spirit

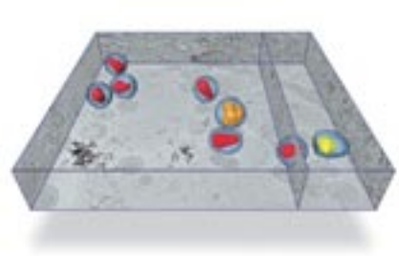
The Tecnai G² Spirit is optimized for the stringent demands of life science and soft matter research where both imaging and analysis is required. Specifically suited for low contrast samples, the BioTWIN lens configuration enables high-contrast imaging for beam sensitive biological specimens. The TWIN lens configuration is for general high-resolution imaging purposes. The Spirit enables 2D and 3D ultra-structure exploration of cells and cell constituents, morphology, chemical composition and function of natural or artifical materials. With fully embedded CCD cameras and STEM detectors, plus Xplore*3D*™ tomography software, the system is a complete and intelligent 3D imaging solution for data collection, reconstruction, visualization and analysis.



Nerve biopsy from a patient with a peripheral neuropathy, thought to be due to a circulating antibody against a component of myelin. This induces a focal increase in the periodicity of myelin with an increase in the width of the intraperiod line. This pathological change does not effect all nerve fibers and can be very accurately diagnosed by TEM.

Image courtesy of Dr. Wayne Moore and Ms. Susan Shinn, ICORD (International Collaboration on Repair Discoveries) and Department of Pathology and Laboratory Medicine, Vancouver General Hospital and the University of British Columbia, Vancouver, BC, Canada.

High resolution TEM techniques have played a valuable role in the investigation of virus structure, and have also proven themselves to be a practical tool for the diagnosis of infectious diseases. For example, TEM helped to establish HIV as a member of the Lentivirus family of retroviruses, and has been used to successfully identify a variety of pathogens in tissue specimens from HIV-infected patients.



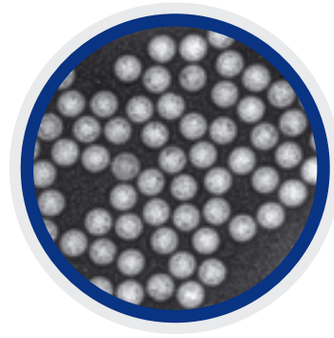
Structures of HIV-1 virus like particles, as determined by electron cryo-tomography. Image courtesy of Elsevier, JMB, Vol 346, Issue 2, 2005.

Virology - looking into viruses

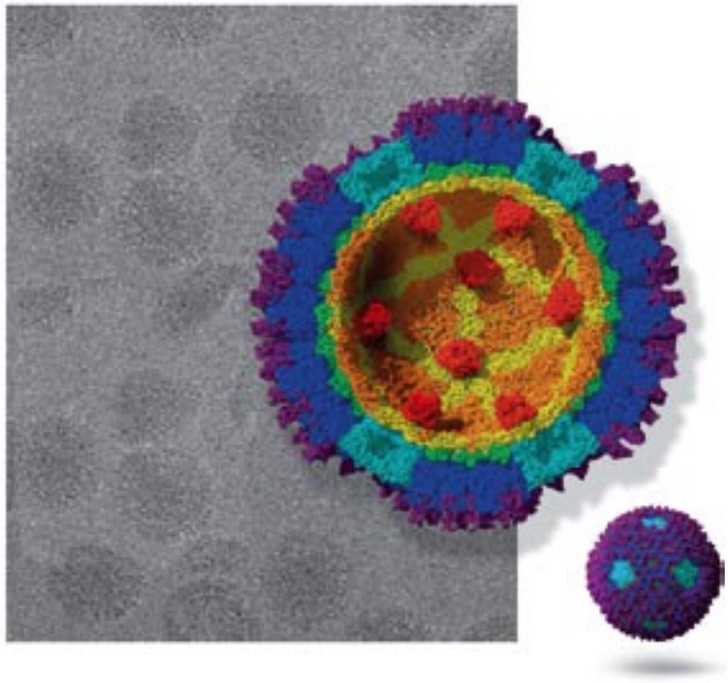
TEM is also an important tool in pharmaceutical quality assurance, enabling fast, positive detection of viral contamination, and allowing rapid determination of a virus family prior to further PCR analysis. It is also the technology of choice for recognizing and quantifying virus-like particles, and monitoring their evolution over time.

Monitoring viral contamination in biopharmaceuticals

TEM techniques provide a rapid, positive alert of viral infection in biotherapeutic drugs, and is also the quickest way to identify the virus family.



Sample of Rota virus.
Courtesy of Cynthia Goldsmith, Centers for Disease Control and Prevention, Atlanta, GA, USA.



Reovirus-Polymerase. Cross-section of a reovirus shows features down to 7.6-Ångström resolution, a scale that reveals the inner features of the viral particle. Visible for the first time within the virus are several tiny 'factories', shown here in red, which convert raw materials from a victim cell's interior into RNA messages instructing the cell to begin manufacturing more viruses. Image is courtesy of Purdue University, Department of Biology, sample courtesy of Xing Zhang, Stephen B. Walker, Paul R. Chipman, Timothy S. Baker, Department of Biological Sciences, Purdue University and Max L. Nibert, Department of Microbiology and Molecular Genetics, Harvard Medical School.

Whether your research goal is immediately achievable or a distant dream, we're ready to work with you to turn your ideas into reality. FEI has experience in providing solutions to the life sciences market and the largest installed base of research grade TEM, SEM and sample prep systems. We're at home in the nanoscale, and can guide you through its intricacies, and its wonders.

Explore discover build - get to the future faster

Multi-discipline collaboration

An important consequence of the cross-discipline nature of NanoBiology is the need for collaboration among researchers in various fields. FEI has taken a leadership role with the development of R&D hubs for collaboration and support in North America, Europe and Asia. In these state-of-the-art NanoPorts, our experts in nanoscale imaging and analysis work with experts from other fields to develop the tools that will help you achieve tomorrow's breakthroughs.

Our NanoPorts in the United States, the Netherlands and Japan also offer a unique opportunity for you to experience FEI's latest solutions first-hand. By meeting the people who design, develop and make our product families you will gain valuable insight into how FEI will work with you to meet your specific challenges and expectations.

Do you want to take a closer look?

For more information about FEI's products, services and solutions for life science discovery, please visit us at www.fei.com, or contact your local sales office.

About FEI

FEI Company is a global leader in providing innovative instruments for nanoscale imaging, analysis and prototyping. FEI focuses on delivering solutions that provide groundbreaking results and accelerate research, development and manufacturing cycles for its customers in life sciences, semiconductor and data storage, academic and industrial R&D markets. With R&D centers in North America, Europe, and India, and sales and service operations in more than 50 countries around the world, FEI's Tools for Nanotech™ are bringing the nanoscale within the grasp of leading researchers and manufacturers. More information can be found online at: **www.fei.com**

FEI Company
World Headquarters
and North American Sales
5350 NE Dawson Creek Drive
Hillsboro, OR 97124-5793 USA
Tel: +1 503 726 7500
Fax: +1 503 726 7509

European Sales
Tel: +31 40 23 56 110
Fax: +31 40 23 56 612

Asia-Pacific Sales
Tel: +65 6272 0050
Fax: +65 6272 0034

Japan Sales
Tel: +81 3 3740 0970
Fax: +81 3 3740 0975

Info: fei.com/sales
www.fei.com

TÜV Certification for design, manufacture, installation and support of focused ion- and electron-beam microscopes for the NanoElectronics, NanoResearch and NanoBiology markets.

02MB-OT0113 04/07

FEI COMPANY™
TOOLS FOR NANOTECH