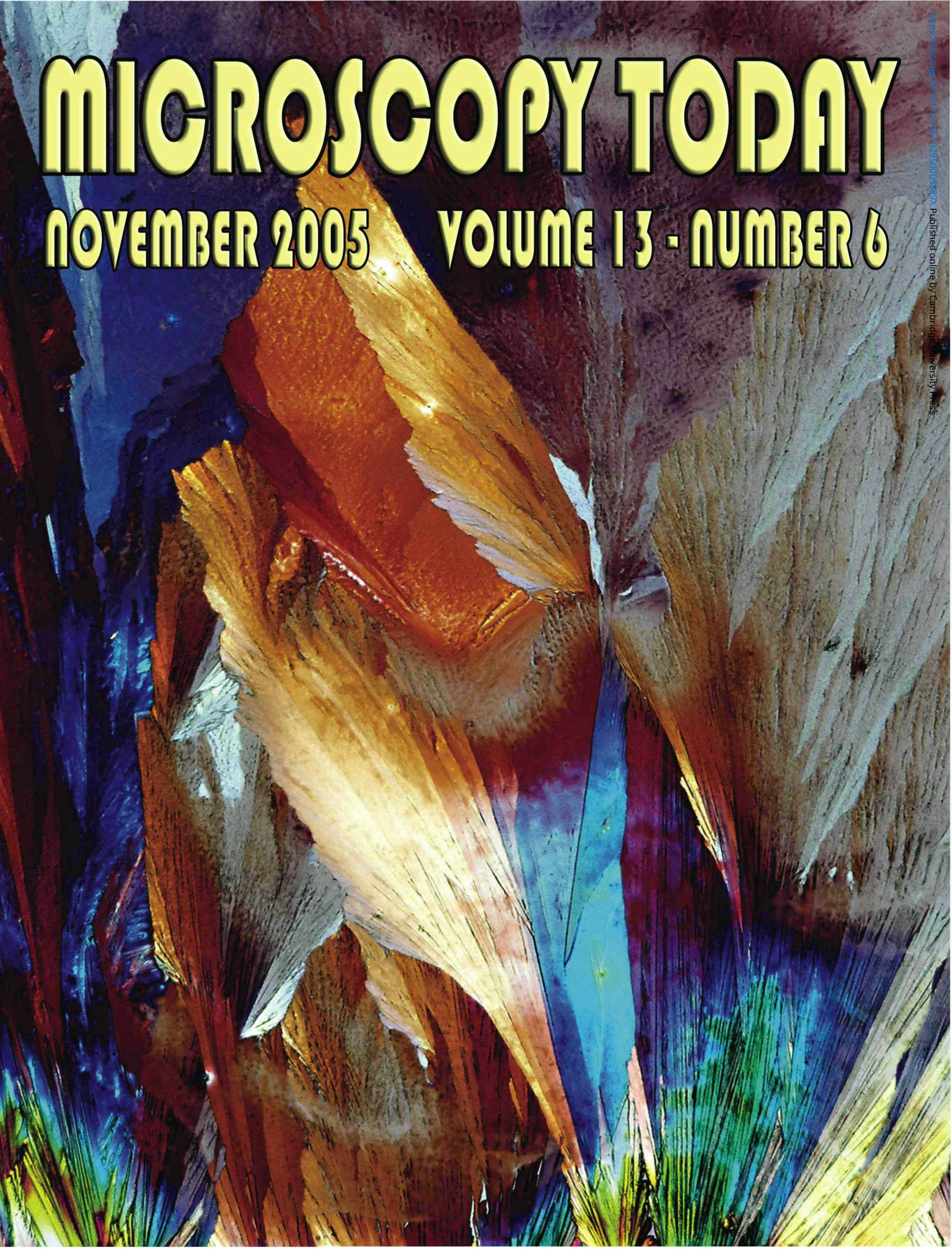


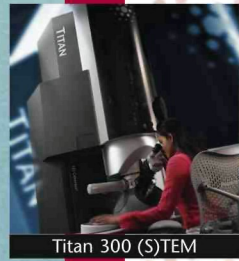
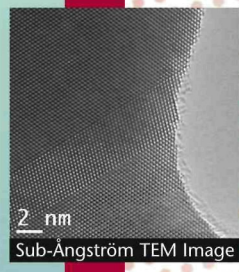
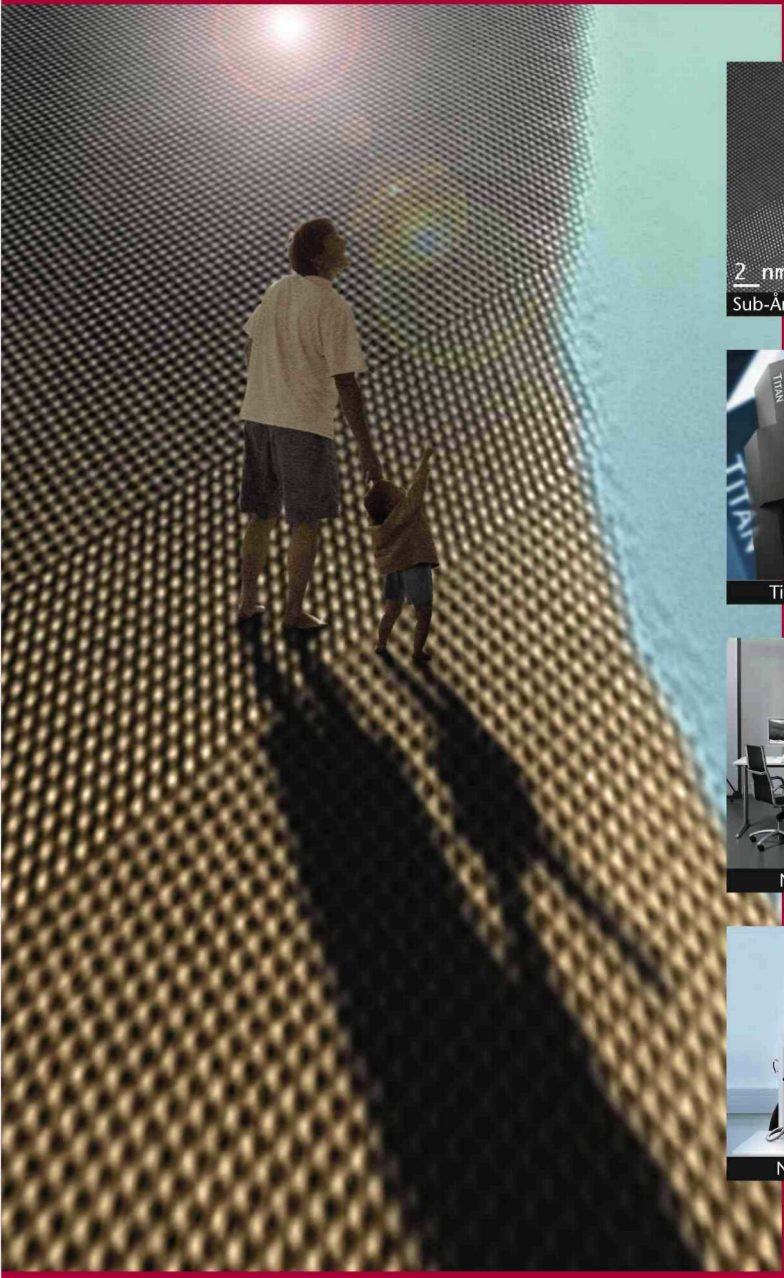
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Very Cool Clathrin

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Clathrin-coated vesicles are the shuttle containers within cells. The vesicles carry lipids and proteins between membrane-bound compartments. Clathrin forms a cage-like structure around the membrane-bound vesicle that is pinched off from the plasma membrane (in endocytosis) or a membranous component of the cytoplasm. Clathrin recruits cargo that is within a vesicle through intermediary proteins known as adaptors that help select membrane-anchored protein and form an interface between the clathrin cage and the membrane bilayer. Whereas many earlier studies have elucidated much of the structure of clathrin, a recent electron cryo-microscopy study by Alexander Fotin, Yifan Cheng, Pitor Sliz, Nikolous Grigorieff, Stephen Harrison, Thomas Kirchhausen, and Thomas Walz provides information on a sub-nanometer scale.² In the same issue of *Nature*, the same laboratory group described the structure of an auxilin-bound clathrin coat and the implications for the mechanism of uncoating,³ but this article will not be discussed in this column.

Clathrin-coated vesicles vary in a dynamic, as well as a static manner. The dynamic requirement is involved when a piece of membrane is pinching off to form a vesicle. The static phase relates to the various sizes of clathrin-coated vesicles. The clathrin molecule is a trimer of three long subunits that radiate symmetrically from a central hub. Each subunit has characteristic straight regions and bends that I will refer to by homology to the lower limb: a thigh (Fotin *et al.* call it the “proximal segment”), knee, leg (“distal segment”), ankle, hindfoot (“linker”), and forefoot (“terminal domain”). These trimers can assemble *in vitro* into small, medium, or larger cages, the latter two being the most common. Fotin *et al.* called the medium-sized structures “hexagonal barrels” and the larger ones “soc-

cer balls.” They reconstituted coats from purified clathrin and adaptor complexes *in vitro* that provided relatively homogeneous specimens with predominately barrels, suitable for electron cryomicroscopy. Images were initially reconstructed at 2.1 nanometers (nm), but by averaging many images, creating density maps, and other manipulations, they were able to achieve a remarkable resolution of 0.79 nm!

The interactions of the trimers were studied in detail. Fotin *et al.* wanted to describe how an assembling cage adapts to cargoes of different sizes and shapes and how the assembly of such an elaborate lattice can be modulated by interactions with regulatory factors. To summarize a complicated description, there are two basic mechanisms at work. One is that individual trimers are flexible, specifically at the knee, ankle, and hindfoot. The hub is relatively inflexible. The second mechanism involves the fitting together of neighboring trimers. They can be arranged at sharp angles to each other, creating a small ball, they may even be arranged in a flat extended array, or various-sized spherical structures in between. They apparently can transition from one configuration to another to fit dynamic requirements during endocytosis.

Clathrin plays several important functions in shuttling cargo within cells. This elegant study by Fotin *et al.* goes a long way in explaining how this molecule can be so versatile in order to play different roles. ■

References

- 1 The author gratefully acknowledges Dr. Stephen Harrison for reviewing this article.
- 2 Fotin A., Y. Cheng, P. Sliz, N. Grigorieff, S.C. Harrison, T. Kirchhausen, and T. Walz, Molecular model for a complete clathrin lattice from electron cryomicroscopy, *Nature* 432:573-579, 2004.
- 3 Fotin A., Y. Cheng, N. Grigorieff, T. Walz, S.C. Harrison, and T. Kirchhausen, Structure of an auxilin-bound clathrin coat and its implications for the mechanism of uncoating, *Nature* 432:649-53, 2004.

INDEX OF ARTICLES

Very Cool Clathrin	3	Fostering LIMS Development Through Open Standards	44
Stephen W. Carmichael, Mayo Clinic		Avrum Goodblatt, U. Penn School of Medicine, Philadelphia	
Metallography for the European Copper Age: Research on the Axe-Blade of the Glacier-Mummy from the Ötztaler Alps in Tyrol ..	8	50th Anniv. Celebrations of Atomic-Resolution Imaging	46
Gerhard O. Sperl, Institute for Historical Materials, Leoben, Austria		Thomas F. Kelly and Allan J. Melmed	
Microscopy and Microbes at Plum Island: Protecting America's Livestock	16	Attaching Spheres to Cantilevers for Colloidal Probe Force Measurements: A Simplified Technique	48
Thomas G. Burrage, Plum Island Animal Disease Center, NY		Yang Gan, University of Newcastle, Callaghan, NSW, Australia	
Color Metallography	22	Nissl: The Man, The Stain and The Substance	50
George F. Vander Voort, Buehler Ltd, Lake Bluff, Illinois		John A. Kiernan, The Univ. of Western Ontario London, Canada	
Characterization of Solids from Oilfield Emulsions	28	Industry News	52
Richard W. Cloud,† Rebecca L. Ramsey,‡ Robert A. Pultz,‡ and Michael K. Poindexter,† Nalco Company, Naperville, Illinois; ‡ Nalco Energy Services, Sugar Land, Texas		NetNotes	56
Automated, Robotic Preparation of Vitrified Samples for 2D and 3D Cryo Electron Microscopy	32	Index of Advertisers	62
P. M. Frederik ¹ and M.H. Storms ² ; ¹ Univ. Maastricht, The Netherlands, ² FEI Company, Achtseweg Noord Eindhoven, The Netherlands			
Ex-Situ “Auto Lift” Technique for TEM Sample Preparation	40		
Garth “Brian” Cook, Micro Optics of Florida, Davie, Florida			
Writing Nano-Scale Patterns on Insulators Using Variable Pressure Electron-Beam Lithography	42		
Floyd Miller and David Frey,* Lehigh University Bethlehem, PA and *Carl Zeiss SMT Inc.			
Microscopy for Children	43		
Caroline Schooley, MSA Project MICRO			

ABOUT THE COVER

From Saunders' “Under the Influence Collection.” November's cover is the image of crystals formed from the mix of several rums influencing the crystallization of a vitamin substrate. “Why rum – spending time in Halifax, NS where rum-runners of “yore” smuggled this nectar of the Caribbean past the revenue cutters, this image takes me home. The “hard part” is getting to the last few drops from which to make the crystal. (Zeiss Axiophot, 5/0.15 PlanNeofluar, Transmitted, Cross Pol., 1st order red + a few tricks—no manipulation of the final image. Fuji Realla ASA 100 neg. Final Image 44x65 inch Giclee on canvas.) ...T.H. Saunders