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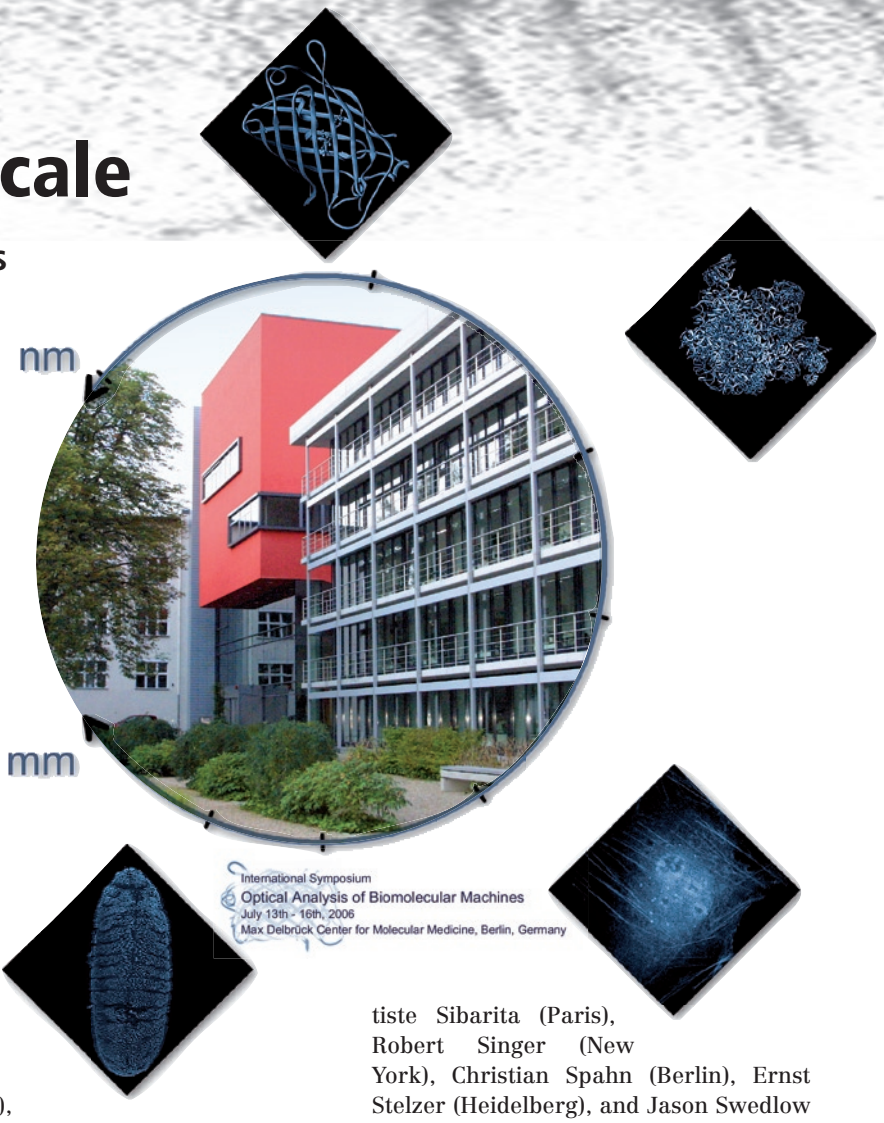
Towards Cellular Imaging at Nanoscale

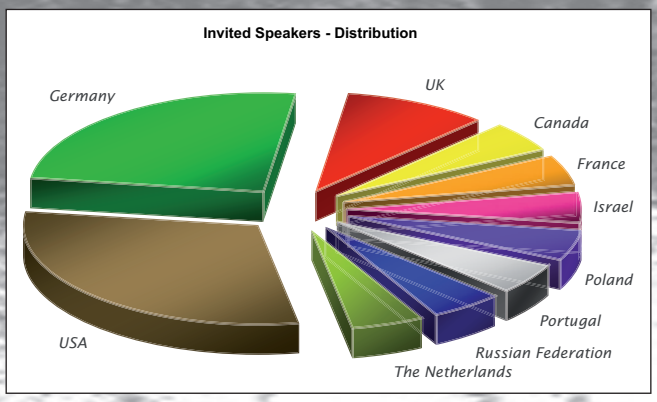
Closer Look at Biomolecular Machines

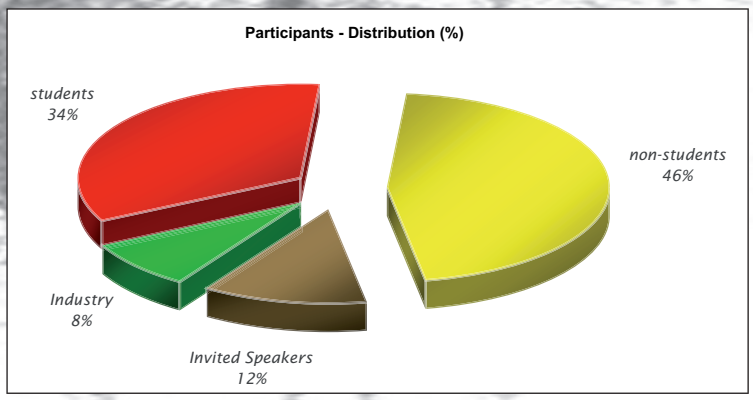


The international symposium on the optical analysis of biomolecular machines held at the Max Delbrück Center in Berlin from 13–16 July 2006 (www.spp1128.uni-hd.de/symposium2006/index.html) united about 150 cutting edge scientists in this field from all over the world, from the Californian West Coast to the New England East Coast to Europe to Japan.

The organizers of the international symposium were M. Cristina Cardoso (Max Delbrück Center for Molecular Medicine, Berlin) and Christoph Cremer (University of Heidelberg). The symposium was held in the context of the Priority Program "Optical Analysis of Supramolecular Biological Complexes" of the German Research Foundation (DFG). Key speakers were David Bazett-Jones (Toronto), Maria Carmo-Fonseca (Lisbon), Jurek Dobrucki (Krakow), Scott Fraser (Pasadena), Stan Gorski (Bethesda), Rainer Heintzmann (London), Stefan Hell (Göttingen), Roger Kornberg (Stanford), Heinrich Leonhardt (Munich), Konstantin Lukyanov (Moscow), Erik Manders (Amsterdam), Thoru Pederson (Worcester), Antonio Politi (Berlin), Carsten Schultz (Heidelberg), Yaron Shav-Tal (Ramat-Gan), Jean-Baptiste Sibarita (Paris), Robert Singer (New York), Christian Spahn (Berlin), Ernst Stelzer (Heidelberg), and Jason Swedlow (Dundee). Topics covered microscopic cellular imaging from the 1 nanometer scale to the millimeter scale, including dynamic analysis in vivo and molecular labeling, as well as correlation of light microscopy and kinetic modelling.

The meeting was complemented by an informative industrial exhibition includ-





ing about 14 different exhibitors from microscope and camera manufacturers, to lasers, microscope incubation chambers and fluorescent labels.

The keynote lecture was held by Professor Roger Kornberg of Stanford University (USA). Among other achievements, he isolated, reconstituted and analysed the protein machinery that turns genes on. He presented the various steps of RNA polymerase interaction with the DNA at subnanometer resolution providing an unprecedented insight into the mechanism of this fundamental process that plays a central role in development, growth and differentiation of cells.

Biomolecular Machines and Optical Resolution

A main topic addressed at the Symposium was the fundamental problem how to extend the range of structural analysis by light microscopy. As postulated in 1873 by the Jena physicist Ernst Abbe, the optical resolution limit of light microscopy corresponds to about half of the wavelength used. In practice, this means a limit of about 200 nm. This limit was regarded to be due to the wave character of light and thus to be an unsurmountable law of Nature. Since biomolecular machines are smaller, this appeared to make impossible any light optical structural analysis of such complexes. Various ways were discussed how to overcome this fundamental problem, not by challenging the Abbe law but by using other light optical ways based on fluorescence excitation, focusing and non-focusing laseroptical scanning devices and refined novel tools of molecular labeling. The Symposium revealed that now such light optical procedures cover the entire range of nanostructural resolution needed, starting from improvement of conventional confocal microscopy to the 100 nm optical resolution range to a size resolution of few tens of nm by structured illumination procedures to Stimulated Emission Depletion (STED) microscopy, with an optical resolution of about 15 nm, or about 1/50 of the exciting wavelength used.

In addition to the structural analysis of biomolecular machines, it is of utmost biological importance also to know where they are in the context of cells within tissues. Also here, novel laser microscopy tools were presented to allow high spatial and temporal resolution “slit scan imaging” as well as single plane illumination imaging of cells and entire small organisms.

Other featured topics included modeling (i.e. the theoretical description of cellular processes) and kinetics (the time-dependent analysis of certain cellular processes). Here emphasis was on the application of fluorescence correlation spectroscopy, single molecule tracing as well as photobleaching and photoactivation techniques in living cells to study the dynamics of cellular biomolecular machines. Data generated from such experiments provide the basis to develop and test theoretical models. In this context, models describing several fundamental processes in the cell were presented and discussed.

All this progress of optical technology, however, would not help much without the appropriate tools of molecular labeling. Thus, many contributions covered new molecular labels that identify specific cellular structures, especially in the living cell, including novel photoswitchable dyes that change color upon illumination.

All participants selected out of 80 posters the three best presentations, which received prizes sponsored by the German Society for Cell Biology and the Nature Reviews Molecular Cellular Biology.

The great challenge of the future will be to further develop and introduce these novel optical and labeling tools into the biomedical community. A challenging highly innovative technical goal for the imaging community might be to develop within the next ten years a light optical “nanoscope” system allowing imaging of multispectrally labeled cellular nanostructures at an optical resolution of 20 nm, a topological resolution (positions, distances of individual molecular subunits within biomolecular machines) down to the 1 nm scale, and a time resolution down to the nanosecond range.

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