Microtubules and Motor Proteins
Douglas McCormick and Bruce Perry

So far in 2007, the NIH has made 349 grants (totaling $110,630,491) for research projects that include studies of microtubules and motor proteins. The National Institute of General Medical Sciences was by far the largest supporter of such research, awarding $43.9 million, followed by the National Cancer Institute ($13.1 million) and the National Institute of Neurological Disorders and Stroke ($12.8 million).

The largest grants in this category include:

Load-induced Cardiac Hypertrophy in the Adult Mammal  $2,169,569
(SP01HL04878-15, National Heart, Lung, and Blood Institute, 08/10/07)
George Cooper (Medical University of South Carolina, Charleston, SC)
Goal: To discover how increased hemodynamic load interacts directly with the heart to explain the causes and consequences of cardiac hypertrophy. Component projects will investigate the induction signals and pathways causing load-induced cardiac hypertrophy in the adult, and its consequences, focusing on mechanisms by which changes in structural and regulatory factors, both intracellular and extracellular, alter contractile function and its regulation in hypertrophy.

Probing Cell Division with Synthetic Chemistry  $2,118,482
(SP01CA078048-09, National Cancer Institute, 05/01/07)
Timothy J. Mitchison (Harvard University Medical School, Boston, MA)
Goal: To develop a "chemical genetics" approach to solving mechanisms in cell biology using small-molecule tools, and to discover small-molecule tools that perturb cell division by novel mechanisms (including identifying target protein/small-molecule pairs as starting points for anti-mitotic drug design). The project optimizes diversity-oriented synthesis (DOS) pathways to generate large libraries of structurally diverse small molecules with complex stereochemistry, and will begin with optimization of a DOS-generated compound that targets Eg5, a motor protein required for cell division.

Liver Cell Membrane Protein—Expression and Function  $1,736,218
(2P01DK041918-16, National Institute of Diabetes and Digestive and Kidney Diseases, 07/03/07)
Allan W. Wolff (Yeshiva University, New York, NY)
Goal: To continue interdisciplinary investigation of the functions and trafficking of specific liver cell membrane proteins, addressing such issues fundamental to liver pathology as: mechanisms of membrane protein trafficking on specific cytoskeletal elements; expression and trafficking of connexins; identification of trafficking steps in endocytosis mutants; and mechanisms of trafficking to autophagic vacuoles and lysosomes.

Electron Microscopy of Biological Macromolecules  $1,697,699
(5P01GM051487-12, National Institute of General Medical Sciences, 05/01/07)
Kenneth H. Downing (University of California, Lawrence Berkeley Laboratory, Berkeley, CA)
Goal: To pursue structural biology research using—and advancing—electron diffraction and electron microscopy. Component projects will address: the structure of tubulin and its interactions with ligands and other proteins that affect the dynamics of the microtubule cytoskeleton; condensins, responsible for condensation of chromatin; and the conformational changes that follow nucleotide hydrolysis in tubulin or that occur upon binding of drugs that inhibit polymerization.

Integration and Control of Molecular Motors  $1,410,491
(5P01AR051174-04, National Institute of Arthritis and Musculoskeletal and Skin Diseases, 03/29/07)
Yale E. Goldman (University of Pennsylvania, Philadelphia, PA)
Goal: To study the actin-based motors—myosin I, myosin V, and myosin VI—and the microtubule-based motor cytoplasmic dynein (with its accessory protein complex, dynactin), via a battery of state-of-the-art approaches: single-molecule fluorescence polarization, nanometer-resolved fluorophore localization, infrared optical traps, rapid biochemical reaction kinetics, nanosecond time-resolved fluorescence anisotropy, dynamic light scattering, genetic manipulations, and detailed electron and atomic force microscopy.

Tau and Neurodegeneration II: A Therapeutic Target  $1,316,477
(5P01AG017216-08, National Institute on Aging, 09/05/07)
Dennis William Dickson (Mayo Clinic College of Medicine, Jacksonville, FL)
Goal: To identify modifiers that influence the progression of microtubule-associated tau protein pathology in human neurodegenerative disease (such as Alzheimer’s disease, progressive supranuclear palsy, and corticobasal degeneration) and to identify therapeutic targets that will form the basis for eventual patient treatments. Subprojects will use a genetic approach to identify tau gene variants that increase the risk for developing 4R tauopathy, use a cell-culture model of early-stage tau filament formation and pathogenesis to study the impact of several factors that have been suggested as causes of tauopathy (e.g. oxidative stress, proteasome inhibition), and employ transgenic mouse models of tauopathy already developed by the program.

Pathological and Functional Impact of Tauopathy In Vivo  $1,271,138
(5P01NS048447-04, National Institute of Neurological Disorders and Stroke, 07/10/07)
Karen E. Duff (New York State Psychiatric Institute, New York, NY)
Goal: To understand how tau becomes pathogenic, and how pathogenic tau disrupts the normal functioning of the neuron ultimately leading to its death. The research will examine gene profiles in single neurons with and without neurofibrillary pathology at different stages to: identify what pathways are affected during the disease process; look at tau turnover and transport; study the effect of tauopathy on neuronal integrity using in vivo imaging; put these observations into functional context by examining how pathogenic tau formation impacts system integrity; and examine the contribution of phosphorylation or aggregation to the pathogenic process. The research will also test therapeutic agents that target these systems.

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