Nobel Laureates in Physiology or Medicine in 2013

The Nobel Prize in Physiology and Medicine is awarded annually by the Swedish Karolinska Institute to scientists and doctors in the various fields of physiology and medicine. It is one of the five Nobel Prizes established by the 1895 will of Alfred Nobel who died in 1896, awarded for outstanding contributions in chemistry, physics, literature, peace, physiology and medicine. Since 1901 the Nobel Prize has been awarded to scientists who have made the most important discoveries for the benefit of mankind.

The 2013 Nobel Prize in Physiology and Medicine was awarded jointly to *James E. Rothman, Randy W. Schekman and Thomas C. Südhof* for their discoveries of machinery regulating vesicle traffic, a major transport system in our cells.

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The medicine prize honored breakthroughs in understanding how key substances are moved around and within a cell and how the cell organizes its transport system. Each cell is a factory that produces and exports molecules. For instance, insulin is manufactured and released into the blood and chemical signals called neurotransmitters are sent from one nerve cell to another. These molecules are transported around the cell in small packages called vesicles. The three Nobel Laureates have discovered the molecular principles that govern how this cargo is delivered to the right place at the right time in the cell. The main problem was to understand how cargo is transported in the cell. In a large and busy port, systems are required to ensure that the correct cargo is shipped to the correct destination at the right time. The cell, with its different compartments called organelles, faces a similar problem: cells produce molecules such as hormones, neurotransmitters, cytokines and enzymes that have to be delivered to other places inside the cell, or exported out of the cell, at exactly the right moment. Timing and location are everything. Miniature bubble-like vesicles, surrounded by membranes, shuttle the cargo between organelles or fuse with the outer membrane of the cell and release their cargo to the outside. This is of major importance, as it triggers nerve activation in the case of transmitter substances, or controls metabolism in the case of hormones. It was a mystery how do these vesicles know where and when to deliver their cargo?

Randy Schekman was fascinated by how the cell organizes its transport system and in the 1970s decided to study its genetic basis by using yeast as a model system. In a genetic screen, he identified yeast cells with defective transport machinery, giving rise to a situation resembling a poorly planned transport system. Vesicles piled up in certain parts of the cell. He found that the cause of this congestion was genetic and went on to identify the mutated genes. Schekman identified three classes of genes that control different facets of the cell's transport system, thereby providing new insights into the tightly regulated machinery that mediates vesicle transport in the cell.

James Rothman was also intrigued by the nature of the cell's transport system. When studying vesicle transport in mammalian cells in the 1980s and 1990s, Rothman discovered that a protein complex enables vesicles to dock and fuse with their target membranes. In the fusion process, proteins on the vesicles and target membranes bind to each other like the two sides of a zipper. The fact that there are many such proteins and that they bind only in specific combinations ensures that cargo is delivered to a precise location. The same principle operates inside the cell and when a vesicle binds to the cell's outer membrane to release its contents. In essence, Rothman dissected the mechanism for vesicle transport and membrane fusion, and through biochemical studies proposed a model to explain how vesicle fusion occurs with the required specificity.

It turned out that some of the genes Schekman had discovered in yeast coded for proteins corresponding to those Rothman identified in mammals, revealing an ancient evolutionary origin of the transport system. Collectively, they mapped critical components of the cell's transport machinery.

Thomas Südhof was interested in how nerve cells communicate with one another in the brain. The signaling molecules, neurotransmitters, are released from vesicles that fuse with the outer membrane of nerve cells by using the machinery discovered by Rothman and Schekman. But these vesicles are only allowed to release their contents when the nerve cell signals to its neighbors. How is this release controlled in such a precise manner? Calcium ions were known to be involved in this process and in the 1990s, Südhof searched for calcium sensitive proteins in nerve cells. He identified molecular machinery that responds to an influx of calcium ions and directs neighbor proteins rapidly to bind vesicles to the outer membrane of the nerve cell. Südhof elucidated how calcium regulates neurotransmitter release in neurons and discovered that complexin and synaptotagmin are two critical proteins in calcium-mediated vesicle fusion. The zipper opens up and signal substances are released. Südhof′s discovery explained how temporal precision is achieved and how vesicles' contents can be released on command.

Randy Schekman discovered a set of genes that were required for vesicle traffic. James Rothman unraveled protein machinery that allows vesicles to fuse with their targets to permit transfer of cargo. Thomas Südhof revealed how signals instruct vesicles to release their cargo with precision. Through their discoveries, ***Rothman, Schekman*** and ***Südhof*** have revealed the exquisitely precise control system for the transport and delivery of cellular cargo. Disturbances in this system have deleterious effects and contribute to conditions such as ***neurological diseases, diabetes,*** and ***immunological disorders.***

By studying the genetic and morphologic study of these mutants, Schekman discovered vesicle intermediates in the traffic between the endoplasmic reticulum (ER) and Golgi apparatus. Importantly, the sec17 and sec18 mutants accumulated small vesicles implicating a role in vesicle fusion.

The work of Rothman, Schekman and Südhof has unraveled machinery that is essential for routing of cargo in cells in organisms as distantly related as yeast and man. These discoveries have had a major impact on our understanding of how molecules are correctly sorted to precise locations in cell. In the light of this, it comes as no surprise that defects at any number of steps in the machinery controlling vesicle transport and fusion are associated with disease.

Vesicle transport and fusion are essential for physiological processes ranging from control of nerve cell communication in the brain to immunological responses and hormone secretion.

Through their discoveries, ***Rothman, Schekman*** and ***Süedhof*** have revealed the exquisitely precise control system for the transport and delivery of cellular cargo. Deregulation of the transport system is associated with disease in these areas. Disturbances in this system have deleterious effects and contribute to conditions such as neurological diseases, diabetes and immunological disorders. For example, metabolic disorders such as type 2 diabetes are characterized by defects in both insulin secretion from pancreatic beta-cells and insulin-mediated glucose transporter translocation in skeletal muscle and adipose tissue. Furthermore, immune cells in our bodies rely on functional vesicle trafficking and fusion to send out substances including cytokines and immunologic effectors molecules that mediate.

In diabetes furthermore, for example, cells can't ingest sugar because transporters that normally reside on the cell surface and import the sugar are stuck inside. Drug makers could potentially improve insulin release and target the machinery that feeds the cell. As mentioned, the groundbreaking discoveries of these three Nobel Laureates have completely changed our view on a fundamental process in cell physiology. Their public health breakthrough has had a major impact on our understanding of how cargo is delivered with timing and precision within and outside the cell. Vesicle transport and fusion operate, with the same general principles, in organisms as different as yeast and man. The system is critical for a variety of physiological processes in which vesicle fusion must be controlled, ranging from signaling in the brain to release of hormones and immune cytokines. Defective vesicle transport occurs in a variety of diseases including a number of neurological and immunological disorders, as well as in diabetes. Without this wonderfully precise organization, the cell would lapse into chaos.

James E. Rothman, Professor of the Biomedical Sciences at Yale University, one of the world's most distinguished biochemists and cell biologists, was born 1950 in Haverhill, Massachusetts, USA. He is Chairman of the Yale School of Medicine's Department of Cell Biology and is the Director and founder of the Biodesign Institute on Yale's new West Campus. Rothman received his PhD from Harvard Medical School in 1976, was a postdoctoral fellow at Massachusetts Institute of

Technology, and moved in 1978 to Stanford University in California, where he started his research on the vesicles of the cell. Rothman has also worked at Princeton University, Memorial Sloan-Kettering Cancer Institute and Columbia University. In 2008, he joined the faculty of Yale University in New Haven, Connecticut, USA, where he is currently Professor and Chairman in the Department of Cell Biology.

Randy W. Schekman was born 1948 in St Paul, Minnesota, USA, studied at the University of California in Los Angeles and at Stanford University, where he obtained his PhD in 1974 under the supervision of Arthur Kornberg (Nobel Prize 1959) and in the same department that Rothman joined a few years later. In 1976, Schekman joined the faculty of the University of California at Berkeley, where he is currently Professor in the Department of Molecular and Cell biology. Schekman, an investigator of the Howard Hughes Medical Institute and professor of cell and developmental biology in the Department of Molecular and Cell Biology at the University of California at Berkeley, lectured on «Membrane Transport Vesicles and Human Disease». His work laid the foundation for recombinant expression of important secretor and membrane proteins such as insulin and hepatitis surface antigen in yeast and used for treatment of diabetes and for immunization to protect against infection by hepatitis B virus.

Thomas C. Südhof was born in 1955 in Göttingen, Germany. He studied at the Georg-August-Universität in Göttingen, where he received an MD in 1982 and a Doctorate in neurochemistry the same year. In 1983, he moved to the University of Texas Southwestern Medical Center in Dallas, Texas, USA, as a postdoctoral fellow with Michael Brown and Joseph Goldstein (who shared the 1985 Nobel Prize in Physiology or Medicine). Südhof became an investigator of Howard Hughes Medical Institute in 1991 and was appointed Professor of Molecular and Cellular Physiology at Stanford University in 2008.

Sources:

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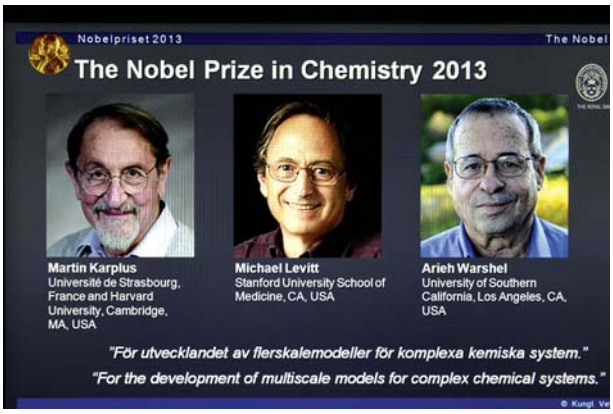
Nobel Laureates in Chemistry 2013

Chemistry was the second prize area that Nobel mentioned in his will. The Nobel Prize in Chemistry has been awarded to 166 Nobel Laureates since 1901.

The Royal Swedish Academy of Sciences has decided to award jointly to ***Martin Karplus, Michael Levitt*** and ***Arieh Warshel*** *«For the development of multiscale models for complex chemical systems»*.



Their work bridges two physical models of understanding the world. *Newtonian mechanics*, with its key concepts of force, mass, and acceleration, has long been used to describe the motion of large entities — the arc of a ball tossed in the air, for instance, or an apple falling from a tree. *Quantum mechanics*, by contrast, describes motion at the level of single atoms and molecules, a minute and bizarre world in which a particle's position is described by a probability, rather than certainty.

Quantum mechanics had always been applied in the domain of the minuscule, and classical physics in the realm of everyday objects, where the inherent randomness of any single particle would disappear once averaged among billions and trillions of other molecules. But ***Karplus*** and his colleagues were interested in large, biological molecules like proteins — too small for any microscope to see, but composed nonetheless of millions of atoms, far too many for any computer to simulate using the complex calculations of quantum mechanics. Newtonian mechanics was not sufficient either, because researchers were interested in molecules in motion — the changes in energy and molecular structure that occur, when a protein recognizes its chemical target, for instance, or an enzyme catalyzes a reaction. «Motions are very important,» said Karplus. «Evolution has made the structure of proteins... so that they have a specific function... What