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Nobel Laureate Michael S. Brown presents Key Note Lecture: How Genes Control Cholesterol

- *Monday 30th May, 2016; 18:40 - 19:40; N. Anitschkow Hall*

A highlight of this year's Congress is a Key Note lecture by Michael S. Brown, Paul J. Thomas Professor of Molecular Genetics and Director of the Jonsson Center for Molecular Genetics at University of Texas Southwestern, Dallas, USA.

Dr. Brown and his long-time colleague, Dr. Joseph L. Goldstein, are recognized as the discoverers of the low density lipoprotein (LDL) receptor, which controls the level of cholesterol in blood and in cells. Drs. Brown and Goldstein have received many awards for this work, including the USA National Medal of Science and the Nobel Prize for Medicine or Physiology in 1985.

Working together, Drs. Brown and Goldstein showed that familial hypercholesterolaemia (inherited high cholesterol) is caused by genetic defects in the LDL receptor, which disrupt the normal regulation of cholesterol metabolism. Their studies led to the elucidation of the mechanism by which this receptor carries LDL particles into cells through coated pits and vesicles. These LDL receptor studies provided clear evidence for selective uptake of macromolecules into cells, giving rise to the concept of receptor-mediated endocytosis. The remainder of this story has been instrumental in changing how hypercholesterolaemia is managed, and paving the way for innovative new therapeutic agents targeting LDL cholesterol.

More recently, study of another genetic disease called Niemann-Pick C (NPC), has provided insights into how cholesterol is transported from one organelle to another, thereby ensuring consistency in cholesterol concentration in the plasma membrane. Extensive studies showed that both the NPC1 and NPC2 proteins have the capacity for binding LDL cholesterol. Whereas binding of cholesterol to NPC2 is rapid, occurring within minutes, binding to NPC1 is extremely slow, requiring several hours to reach equilibrium. However, this process can be accelerated when cholesterol is delivered by NPC2. Based on these findings, it was proposed that NPC2 extracts cholesterol from LDL in the lysosome and then transfers it to membrane-bound NPC1 for insertion into the lysosomal membrane, currently being tested in the laboratory of Professor Brown.

The work of Drs. Brown and Goldstein has not only been the stimulus for new thinking about cholesterol homeostasis, but also has led to the development of new concepts in biology. Specifically, these include selective sorting of proteins within the plasma membrane, a prerequisite for receptor-mediated endocytosis; receptor-mediated endocytosis and receptor recycling; and, finally, the concept of feedback regulation of receptors.

Michael S. Brown received an M.D. degree in 1966 from the University of Pennsylvania. He was an intern and resident at the Massachusetts General Hospital, and a post doctoral fellow with Earl Stadtman at the National Institutes of Health. He is currently Paul J. Thomas Professor of Molecular

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