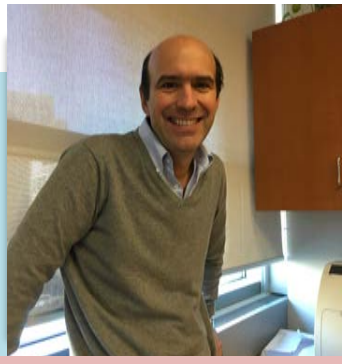
NANYANG TECHNOLOGICAL UNIVERSITY

NTU Institute of Structural Biology

Date: 5 Dec 2016, Monday
Time: 4pm – 5pm
Venue: School of Biological Science
Classroom 1
SBS-CR1

**Speaker:**
Prof. Filippo Mancia
Department of Physiology and Cellular Biophysics, Columbia University, New York

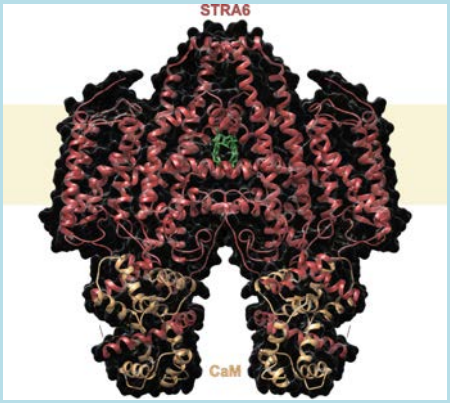
**Host:**
Prof. Daniela Rhodes



# The Molecular Mechanisms Underlying Cellular Uptake of Vitamin A

Many biological processes, including the visual cycle and embryonic development are crucially dependent on an adequate supply of Vitamin A [1]. A cell receives Vitamin A either directly from food intake, or from the liver, released as retinol (vitamin A alcohol; ROH) bound to its carrier retinol-binding protein (RBP, also termed RBP4), which allows the highly hydrophobic retinol to circulate in plasma [2]. Once inside the cell, retinol binds specific intracellular carriers, specifically cellular retinol-binding proteins (CRBPs; [3]).

How retinol is released from RBP and internalized by target cells has been the subject of intense debate. In a landmark study in 2007, the RBP receptor was cloned [4] and found to be a protein encoded by a gene previously identified and classified as stimulated by retinoid acid gene 6 (STRA6). STRA6 is a 75 kDa protein with 9 predicted TM segments, showing no sequence similarity to any known transporter, channel or receptor. However, since then progress in understanding how this system works at a molecular level has been hampered by the absence of an atomic model of STRA6.




We present the structure of zebrafish STRA6 determined to 3.9Å resolution by single-particle cryo-electron microscopy [5]. STRA6 displays one intramembrane and nine transmembrane helices in an intricate dimeric assembly (Fig. 1). Unexpectedly, calmodulin is bound tightly to STRA6 in a non-canonical arrangement. Residues identified with RBP binding map to an arch-like structure that covers a deep lipophilic cleft. This cleft is open to the membrane, suggesting a possible mode for internalization of retinol via direct diffusion into the lipid bilayer.

Figure 1. The cryo-EM structure of STRA6 in complex with calmodulin. STRA6 is the receptor for retinol (vitamin A) bound to its carrier retinol-binding protein. The protein is a dimer (in red), and each protomer binds one molecule of calmodulin (in gold). Two putative cholesterol molecules are shown in green. The approximate location of the membrane is in yellow.

1. Goodman, D.S. (1984). Vitamin A and retinoids in health and disease. N Engl J Med, 310: 1023-31.
2. Soprano, D.R. and Blaner, W.S., Plasma retinol-binding protein., in The Retinoids, Biology, Chemistry and Medicine, M.B. Sporn, A.B. Roberts, and D.S. Goodman, Editors. 1994, Raven Press: New York, NY. p. 257-282.
3. Li, Y., Wongsiriroj, N. and Blaner, W.S. (2014). The multifaceted nature of retinoid transport and metabolism. Hepatobiliary Surg Nutr, 3: 126-39.
4. Kawaguchi, R., Yu, J., Honda, J., Hu, J., Whitelegge, J., Ping, P., Wiita, P., Bok, D. and Sun, H. (2007). A membrane receptor for retinol binding protein mediates cellular uptake of vitamin A. Science, 315: 820-5.
5. Chen, Y., Clarke, O.B., Kim, J., Stowe, S., Kim, Y.K., Assur, Z., Cavalier, M., Godoy-Ruiz, R., von Alpen, D.C., Manzini, C., Blaner, W.S., Frank, J., Quadro, L., Weber, D.J., Shapiro, L., Hendrickson, W.A. and Mancia, F. (2016). Structure of the STRA6 receptor for retinol uptake. Science, 353: