Institute of Medical Biology
A*STAR

Seminar Announcement

- All Are Welcome -

Speaker: **Prof Daniel Cutler**
Professor of Cell Biology UCL & MRC Senior Scientist

Title : ***"Weibel-Palade Bodies; at the Endothelial Interface between Inflammation and Haemostasis"***

Date : **12 November 2012 (Monday)**

Time : **2:00pm – 3:00pm**

Venue : **Breakthrough Theatrette, Matrix Level 4**

Host : **Dr Brian Burke**
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Abstract:

Weibel-Palade bodies (WPB) are the regulated secretory organelles of endothelial cells. These cigar-shaped membrane-bound structures are said to act in First Aid to the vasculature, primarily in Inflammation and Hemostasis, but also in vascular tonicity and angiogenesis. Their content is dominated by the highly multimerised hemostatic protein Von Willebrands factor (VWF), whose coiling into long proteinacious tubules gives the organelle its shape. Another component is the leukocyte receptor P-selectin. This integral membrane protein is delivered to the endothelial surface along with VWF at exocytosis, thus jointly driving the initation of inflammatory and hemostatic processes.

New WPB undergo maturation, aided by their recruitment of Rab27a that anchors them to peripheral actin filaments via its effectors, allowing completion of multimerization of VWF. The multimeric state of VWF is critical- too low and a bleeding disorder will ensue, too high, and excessive thrombosis can be lethal. Loss of Rab27a as in Griscelli's syndrome, leads to release of immature incompletely multimerised VWF that corresponds to that seen in Von Willebrands disease. Actin not only anchors the WPB, but is also actively required for exocytosis of VWF; a transient actin-MyoIIb ring is also used to squeeze the huge VWF multimers out into the plasma.

P-selectin is needed for recruitment and deceleration of leukocytes from flowing plasma to the surface of endothelial cells. To achieve this remarkable feat, the receptor needs to be clustered and this in turn is dependent on the tetraspanin CD63 also found within WPB. In mice, loss of CD63 causes a loss of leukocyte recruitment identical to that caused by loss of P-selectin itself.

Altogether, the complex biogenesis and functioning of these organelles thus places them at the centre of endothelial pro-inflammatory and haemostatic functions.

About the Speaker:

Professor Cutler began to work on membrane trafficking during his PhD, and followed this up with two post-docs in this discipline. During his time in California, he became interested in the targeting and sorting of proteins into regulated secretory organelles in neuroendocrine cells. When he started his own lab at Imperial College, he continued in this area, and eventually worked on targeting of P-selectin into secretory granules. His interest in P-selectin eventually led him to begin the study of the granules of endothelial cells, Weibel-Palade Bodies, where P-selectin is usually found. He has now spent 15 years studying these organelles, investigating not only the basic cell biology of organelle formation but also attempting to understand how that cell biology underpins the medically critical processes that these organelles support.