CENTRE FOR CANCER BIOMEDICINE

# CCB welcomes you to seminar by

# Viola Lobert and Sharmini Alagaratnam

**Tuesday the 25th of October at 13.00 – 14.30**

**In the Auditorium in the Research Building, The Norwegian Radium Hospital**

**Refreshments are served in the lobby after the seminar**

**At 13.00 hrs: Viola Lobert, PhD student, MSc** – Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital

## Regulation of cell migration by post-translational mechanisms

Cell migration is an important aspect of embryonic development, wound healing and immune responses. It also plays a role in pathological processes that include cancer, vascular disease, osteoporosis, chronic inflammatory diseases and mental retardation. This therefore explains the interest in understanding the mechanisms that regulate the cell's ability to move. Intracellular transport of a variety of cell-surface receptors is known to be important for cell migration, and special focus has been given to the integrins. Integrins are extracellular matrix receptors which undergo endocytosis and recycling, and this transport is thought to contribute to the ability of cells to detach and re-attach. Interestingly, we observe that in addition to be recycled, integrins are also degraded in lysosomes, and that this requires their prior ubiquitination. Only fibronectin-bound integrins are ubiquitinated and sorted into multivesicular endosomes (MVEs), and this step requires the endosomal complex required for transport (ESCRT) machinery. We propose that this trafficking route exists in order to prevent endosomal accumulation of ligand-bound integrins that might otherwise form non-productive adhesion sites. Upon ESCRT depletion, integrins accumulate intracellularly together with the nonreceptor tyrosine kinase Src at enlarged early endosomes. This results in the inability of Src to ativate myosin light chain kinase, MLCK, localized at the cell periphery, which thereby cannot phosphorylate the myosin regulatory light chain MRLC. These signaling pathways govern Golgi orientation, focal adhesion turnover and cell spreading, as well as cell migration. Importantly, prior to the initiation of mesenchymal cell migration, epithelial cells need to break their cell-cell contacts, take on mesenchymal characteristics and become invasive, a process known as the epithelial-to-mesenchymal transition (EMT). We have identified a novel role for the phosphatase Pleckstrin Homology domain Leucine-rich repeat Protein Phosphatase PHLPP1 in the regulation of this process. We find that PHLPP1 regulates the recruitment of E-cadherin to cell-cell contacts, and loss of PHLPP1, which occurs in many colorectal cancers, results in increased cell migration and invasion.

**At 13.45 hrs: Sharmini Alagaratnam, Postdoc, PhD** – Department of Cancer Prevention, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital

## Malignancy in pluripotency: Transcriptional studies in embryonal carcinomas and embryonic stem cells

Comparison of the pluripotent embryonic stem (ES) cell-embryonal carcinoma (EC) pair is intriguing, given that the ECs are considered the malignant counterpart of ES cells. We exploited this relationship in a genome-wide study of five EC and 6 ES cell lines, strictly selecting the pluripotent subpopulations in both for gene expression profiling. Against this background of pluripotency, we identified a malignancy signature of 28 differentially expressed genes, in particular two which were higher expressed in EC compared to ES cells, and are also upregulated in primary testicular germ cell tumours (TGCTs). The exon-level resolution of our data also allowed us to detect alternative splicing events/alternative promoters. These events were validated in primary TGCTs, and interestingly showed correlation with the level of differentiation of the tumours studied. This underlines the significance of pluripotency in tumorigenesis, Finally we address the possible role of genomic changes as a driver for changes in gene expression. Given the similarities in genomic gains and losses in EC cells and extensively cultured adapted ES cells, we also undertook an exploratory study to chart how the signature genes vary along the transformation axis normal ES to adapted ES to EC cells.