



**The Department of Mechanical and Manufacturing Engineering is
inviting you to the Doctoral dissertation defense of
Maria Kalli**

**TITLE: Elucidation of the effects of solid stress on fibroblasts and
cancer cells behavior in solid tumors**

Tuesday, 2 April 2019, 9:00 am

**Room: 019, Learning Resource Centre UCY Library "Stelios Ioannou",
New campus**

ABSTRACT:

Apart from cancer cells, solid tumors consist of non-cancerous cells, such as fibroblasts and immune cells, an extracellular matrix (ECM) that forms a network of fibrillar proteins and macromolecular chains, including collagen, hyaluronan and fibronectin, and a vascular system. The excessive production of ECM proteins, a condition known as *desmoplasia*, along with the uncontrolled proliferation of cancer cells in the confined space of the host tissue, leads to the development of compressive forces within the tumor, generating the so-called *solid stress*. Solid stress is a characteristic biomechanical abnormality of several solid tumors, including breast, colon, pancreatic and brain cancer, and it has been previously shown to affect cancer cell proliferation and migration. However, the underlying mechanisms of how it is implicated in tumor progression, and especially in cancer cell metastasis, is not yet fully understood. Moreover, while the effect of solid stress on cancer cells is currently being investigated, there is no pertinent study considering its effect on fibroblasts and whether these effects contribute to tumor progression. The objective of this research was to investigate the implication of solid stress in both cancer cells and fibroblasts. For this purpose, we employed a custom-made device to apply a predefined compressive stress on pancreatic cancer cells and fibroblasts, as well as on brain cancer cells, similar in magnitude to that experienced by cells in native tumors. Our results suggest that solid stress stimulates fibroblasts activation and strongly upregulates Growth Differentiation Factor-15 (*GDF15*) expression. Moreover, co-culture of compression-induced activated fibroblasts with pancreatic cancer cells significantly promotes cancer cell migration, which is inhibited by shRNA-mediated silencing of *GDF15* in fibroblasts. By applying mechanical compression directly on pancreatic cancer cells, we found an increase in their metastatic potential accompanied by a strong upregulation of *GDF15* expression. Subsequently, we identified a solid stress-induced mechanism relied on the Akt/CREB1 pathway that can transcriptionally regulate *GDF15* expression in order to promote cancer cell migration. Finally, we found that solid stress can impair the growth of brain cancer multicellular spheroids and it can differentially regulate their migration and gene expression profile. Even though future studies are needed to reveal a comprehensive mechanism of how solid stress induces the migration of brain cancer cells, our results suggest a novel regulatory role of solid stress in tumor progression, rendering *GDF15* as a potential biomarker for the presence of solid stress *in vivo* and a molecular target for future anti-metastatic therapeutic innovations.

SHORT BIO:

Maria Kalli earned a BS degree in Biological Sciences from the University of Cyprus in 2014. Since 2014 she is a PhD student in the MME Department at the University of Cyprus at the Cancer Biophysics Laboratory. Her main research interest is to identify how mechanical forces that are generated during the growth of solid tumors, can affect the properties of fibroblasts and cancer cells. During her PhD, she was funded by a Scholarship Grant given by University of Cyprus to Doctoral Students and participate in research projects funded by the European Research Council 336839-ReEngineeringCancer. She has co-authored 7 scientific articles in peer-review journals and gave 2 presentations at international conferences.

Supervisor: Dr. Triantafyllos Stylianopoulos, Assistant Professor