University of Cyprus
Department of Biological Sciences

Postgraduate Seminars

Seminar Series 2018-2019

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"PI3K-AKT-mTOR targeting in metastatic prostate cancer"

Wednesday, 3 October 2018, at 17:00
Building CTF 01, Room 108, Panepistimioupoli Campus

This seminar is open to the public

Metastatic prostate cancer is the 2nd commonest cancer in men and a leading cause of cancer-related mortality in the UK. Current clinical trials are investigating the use of PI3K-AKT-mTOR inhibitors in metastatic castration-resistant prostate cancer (CRPC). 50-70% of metastatic CRPC patients have genomic aberrations of the PI3K pathway, mainly involving loss of PTEN, an important negative regulator of the PI3K-AKT pathway. Upregulation of HER3 was previously suggested to be an important resistance mechanism.

During the time course of my research I explored the changes in ErbB expression, activation and heterodimerisation in the context of PI3K-mTOR inhibition in vitro and in vivo. We showed that different ErbB subtypes are upregulated in vitro as part of a potential resistance mechanism in response to PI3K-mTOR inhibition, depending on the cell line PTEN status. Concomitant upregulation of either AR or PSMA was also observed. In PTEN WT prostate cancer cells, the upregulation of PSMA was demonstrated to be HER2 dependent and could be inhibited by lapatinib. The PSMA upregulation was also demonstrated using PSMA PET imaging analyses upon PI3K-mTOR inhibition in vivo in prostate cancer mouse xenograft models. Furthermore, I used fluorescence lifetime imaging microscopy (FLIM) which is the gold-standard technique for measuring Forster resonance energy transfer (FRET). This is an established technology in our laboratory and was used to evaluate HER3 heterodimerisation in prostate cancer cells and mouse xenograft tissue.

The clinical implications of my results propose the use of PI3K-AKT-mTOR inhibitors in the metastatic hormone-sensitive setting as well as in CRPC. In addition, tissue and/or exosomal ErbB heterodimerisation, together with the use of clinically available PSMA imaging probes, might prove an additional biomarker in resistance detection and subgroup classification. Finally, this might allow the design of prospective clinical trials using PSMA-targeted therapies.