THE OHIO STATE UNIVERSITY
COLLEGE OF MEDICINE

Department of Biomedical Informatics

RARg cross-talk with AR in prostate cancer

Abstract: Normal prostate development and homeostasis is regulated by multiple transcription factors (TFs) including the androgen receptor (AR) and other nuclear hormone receptors such as the retinoic acid receptor gamma (RARγ). In prostate cancer (PC) altered stoichiometry between TFs and coregulators converge with epigenetic mechanisms to govern disease progression, and the response to Androgen Deprivation Therapy (ADT). We have focussed on how miR-96 targeting of RARγ, and an interdependent network of proteins including the coactivator TACC1, limits the cross-talk of RAR and AR and changes the response to ADT. Specifically, in non-malignant HPr1AR, and androgen sensitive LNCaP and ADT-resistant 22RV1 cells, we undertook miR-96 mimic-dependent RNA-Seq, coupled with biotinylated miR-96 capture to identify all directly bound and regulated genes (IMPACT-Seq (*i*dentification of *MiRNA* REs by *p*ull-down and *a*lignment of *c*aptive *t*ranscripts—*seq*uencing)). We also used GFP-tagged RARγ for CUT and RUN ChIP-Seq and coimmunoprecipitation and RIME (*R*apid *i*mmuno- precipitation *m*ass spectrometry) to define the RARγ cistrome interactions with the AR, and RARγ protein-protein interactions. MiR-96 regulated transcriptomes were enriched for Androgen, Estrogen and MYC networks, as well as G_2/M checkpoints and the response to Tretinoin (retinoid). IMPACT-seq identified ~750 significant miR-96 binding sites in LNCaP cells, ~ 50% of which were shared. For example, TACC1 was significantly miR-96 downregulated at the mRNA and protein levels, and was directly bound by miR-96, and RARγ and TACC1 physically interact. RIME in LNCaP and 22RV1 revealed that RARγ associated with a number of coregulators that impact AR function including CAND1. Defining the RARγ-AR cistromes revealed that elevated RARγ expression remarkably increased AR binding at active enhancers and significantly increased DHT-dependent gene expression patterns that govern luminal differentiation. Of clinical importance, gain of expression of RARγ and TACC1 changed cell responses to Enzalutamide, the clinically-utilized ADT. Of further clinical relevance, the most altered miR-96 bound and regulated genes, which includes TACC1, clustered tumors from the SU2C cohort and coxph models show these tumors have worse overall survival. Finally, we identified that RARγ functions are in an antagonistic and genomically intertwined relationship with the cut class homeobox factor, ONECUT2, and they function as a transcriptional rheostat to govern cell lineage decisions and miR-96 driven loss of RARγ/TACC1 allows ONECUT2 to function in an unopposed manner to drive ADT-resistant PC.

About the Speaker: Throughout my research career I have sought to understand how disruptions to the epigenome can act as disease-drivers in hormone responsive cancers, with the goal to exploit this understanding in either diagnostic or therapeutic settings. In 2010, I came to the realization that to meet my research goals would require the analyses of high dimensional data, for which I was ill-equipped. Therefore, I undertook mid-career "re-tooling" and completed a Master's in Bioinformatics from Johns Hopkins University. Following this, I have developed strong expertise in translational bioinformatics that centers on the analyses and integration of genomic and epigenomic data sets, and their integration with publicly available data to annotate experimental findings. Over the 20 years since becoming an independent investigator, I have been continually funded by cancer charities and governmental research organizations. Currently, I am funded by the DoD, NCI, NIA and Prostate Cancer UK, and members of my group are supported by Pelotonia training grants. To date I have published more than 130 primary research papers and scientific reviews and my h index is 42 (Google Scholar). I am committed to training successful researchers in cancer biology by applying interdisciplinary training approaches. To date I have directly trained ten MS students, 12 PhD students and eight post-doctoral fellows. Currently, I am supervising three PhD students and two Post-doctoral scientists. All past trainees remain in biomedical research and research-related careers and nine have transitioned to scientific leadership positions.

Moray J Campbell, PhD

Friday, January 15th, 11:00am-12:00pm

Carmen Zoom