Areas of Excellence Scheme – Center for Nasopharyngeal Carcinoma Research
(AoE/M-06/08)

Layman's Summary

Our Center for NPC Research aimed to strengthen ties for Hong Kong's NPC and EBV experts in basic science, clinical practice, and translational studies to improve our basic understanding and clinical care for NPC patients. We established important resources for the NPC/EBV international research community, such as the NPC Tissue Bank with specimens from 5 hospitals to facilitate genomic/biomarker studies. We constructed tissue microarrays important for looking at clinical significance of biomarkers. We established EBV+ NPC cell lines and animal models for drug testing and an NPC Cell Line Repository for NPC and immortalized normal nasopharyngeal epithelium (NPE) cell lines for the research community. Our new EBV+ NPC cell lines were extensively characterized and are excellent models for basic functional studies and preclinical evaluation of novel NPC treatments. We also used them to look into the role of the NPC tumor microenvironment and clinical responses. Understanding the genetic basis of NPC development by identifying key genes and pathways that drive the development and metastatic spread can serve as biomarkers for diagnosis or therapeutic targets. Several new genes were identified and characterized to determine their role in cancer. We studied what determines NPC genetic susceptibility, since people with a family history of NPC have a higher risk for NPC. We utilized next-generation sequencing (NGS) to elucidate genes associated with NPC genetic susceptibility. The top candidate identified was MST1R, which was associated with NPC early-age onset. We studied the MHC region of NPC known to associate with NPC risk and identified novel non-HLA genetic loci associated with NPC risk or protection. Host immune dysregulation by EBV and presentation of the virus to the immune system appear to play important roles in genetic susceptibility. Our global NGS approaches of NPC tumors also identified genetic variants of genes in the NFkB pathway crucial in NPC. Epidemiological methods were used in multi-center case-control studies of NPC in Hong Kong. A novel factor, milk consumption, was identified as associated with lower NPC risk. Vitamin D deficiency was associated with higher NPC risk. Our comprehensive study of 8 regions from 3 continents showed the decline of salted fish consumption cannot fully explain the decline of NPC. Our studies also provide the strongest observational evidence that smoking is a causal factor of NPC. We are contributing to the Chinese NPC GWAS Consortium, which is the largest and most comprehensive NPC study collaboration. EBV plays an important role in NPC development. It contributes to immortalizing and driving cells to cause cancer. EBV is present in all Chinese NPC tumors. We targeted EBV in NPC cells using specific inhibitors to show their usefulness in animal models. We examined the EBV genome diversity in NPC to determine whether there were NPC-specific genetic

variants causing the cancer. The EBV strains present in the saliva of NPC patients and healthy individuals in HK were sequenced; we identified high-risk EBV variants associated with NPC. Dissecting out what attributes of EBV contribute to NPC pathogenesis was also studied using our NPC EBV-infected and uninfected cell lines, immortalized NPE cell lines, as well as genetically engineered EBV, to identify pathways involved in NPC development. EBV BARTs were studied, both as NPC biomarkers and in functional NPC studies. Recent studies indicate that EBV-associated histone marks also play an important role in host gene expression leading to NPC. Basic cancer studies examined how cell replication, chromosome aberrations and DNA replication can contribute to tumorigenesis. Study of protein-protein interactions, functions and regulation of yeast and human DNA replication-initiation proteins led to the discovery of essential features of DNA replication that may be good drug targets. Biomarker studies focused on plasma circulating EBV DNA and viral BARTs, circulating tumor cells, EBV serology, and methylated markers. We studied their usefulness for non-invasive screening for early disease, recurrence, and distant metastasis to improve diagnosis and monitoring the efficacy of cancer treatments of NPC patients. We evaluated novel imaging parameters to improve characterization and prognostication of NPC and distinguish between recurrent NPC vs post-radiotherapy fibrosis to spare patients from over treatment. Our studies identified novel imaging parameters that are able to risk stratify and are of prognostic value for NPC. We tested several preclinical drugs in NPC cell lines and animal models to identify novel useful agents for NPC treatment. Compounds targeting cancer stem cells inhibit growth of EBV+ cells and targeting EBV showed promising results. Anti-cancer drug candidates targeting DNA replication proteins are under study. Clinical studies aimed to optimize treatment of late stage metastatic NPC patients and examined the long-term outcomes of NPC patients.

** The above summary is written mainly by the project team. The views expressed in the summary do not necessarily represent those of the University Grants Committee / Research Grants Council.*