

**LIGHTNING TALKS • DRUG DISCOVERY AND DEVELOPMENT****[LTD 1]****NATURAL HSP90 INHIBITORS AS A POTENTIAL THERAPEUTIC FOR CANCER TREATMENT: A COMPREHENSIVE REVIEW*****Hui Yi Liew, Xin Yoong Tan, Yong Sze Ong, Kooi Yeong Khaw****School of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, Bandar Sunway, 47500 Subang Jaya, Selangor, Malaysia*

Heat shock protein 90 (Hsp90) has evolved as a cancer cell growth regulator by stabilising various oncogenic kinases. Upon blockade of Hsp90, client protein expression is downregulated and leads to denaturation of cellular proteins, thus inducing cancer cell death. Hsp90 inhibitors which are naturally derived from plants, fungi and bacteria have gained substantial interest as a feasible therapeutic approach for cancer treatment. Due to their diverse pharmacological properties, researchers could gain insights on the potential development of more efficacious Hsp90 inhibitors for cancer treatment. Thus, this research was conducted to analyse both *in vitro* and *in vivo* data to provide an in-depth understanding of the chemical and biological activities of natural Hsp90 inhibitors. Comprehensive search was conducted using the PubMed, Scopus and Web of Science databases with search terms “Hsp90 inhibitor” and “cancer”, prompting a total of 61 articles. The efficacy of the naturally derived inhibitors was determined using the concentration of Hsp90 inhibitors needed to reduce the number of cancer cells by half ( $IC_{50}$  values) in *in vitro* studies. A total of 14 classes of natural inhibitors were selected based on the inclusion criteria. Among them, terpenoids exhibited high effectiveness ( $IC_{50}$  less than 5  $\mu$ M) against cancer cells. In addition, some of the natural Hsp90 inhibitors were proven to decrease tumour burden in animal cancer models. It is interesting to note that celastrol, a naturally derived terpenoid, showed the highest efficacy of 80% tumour ablation in pancreatic cancer xenograft mice. The detailed mechanism of action and physicochemical properties of different classes of natural Hsp90 inhibitors were explored in a hope to provide insights for future development and clinical translation.

**LIGHTNING TALKS • DRUG DISCOVERY AND DEVELOPMENT****[LTD2]****PROTECTIVE ROLE OF PHYTOESTROGEN COUMESTROL AGAINST ESTROGEN DEFICIENCY-INDUCED OSTEOPOROSIS IN BONES OF OVARIECTOMISED RATS***Mir Omer Ali, Huma Shahzad**School of Medicine, International Medical University*

Osteoporosis is a common disorder of bones affecting 1 in every 3 women at menopause. Osteoporosis weakens bone by causing loss of bone mass and architecture. This loss might be due to reduced estrogen levels in menopausal women. In some women, hormone replacement therapy (HRT) has been shown to improve bone osteoporotic changes but is also reported to have deleterious effects such as deep vein thrombosis (DVT) and endometriosis. Coumestrol is a naturally occurring phytoestrogen, mimicking the biological activity of estrogen which can be used as an adjunct for the bone loss in menopausal women. Recent studies have shown that Coumestrol may be beneficial to patients with bone resorption disorders. However, the mechanisms underlying the action of Coumestrol is not clarified.

We hypothesised that Coumestrol upregulates estrogen receptors in the bones of postmenopausal rats and the effect is mediated through ER- $\alpha$  or ER- $\beta$ . We also hypothesised that Coumestrol suppresses estrogen deficiency-induced inflammation, RANKL mediated osteoclast differentiation, bone resorption, and increased Wnt signalling in the bones of the postmenopausal osteoporosis rat model.

In this study molecular mechanisms of Coumestrol anti-osteoporotic effects were compared with that of 17 $\beta$ -estradiol (E2, positive control). Two weeks after ovariectomy, adult female SD rats were randomly divided into 5 groups (n=6). The treatment group received Coumestrol at two doses (10 and 20 mg/kg/day) and 17 $\beta$  estradiol at 0.2  $\mu$ g/kg/day subcutaneously for 2 weeks consecutively. At the end of treatment, rats were sacrificed, and samples from the femur were immediately collected and preserved for molecular studies. For the histological study, bone was decalcified in 10 % (w/v) of ethylenediaminetetraacetic acid (EDTA; pH 7.4) for 3 weeks and then embedded in paraffin. The serum was separated from whole blood for the analysis of bone markers and inflammatory mediators.

**LIGHTNING TALKS • DRUG DISCOVERY AND DEVELOPMENT****[LTD3]****THE ROLE OF PARTHENOLIDE IN CYTOTOXIC T-CELL (CTL) RESISTANT NASOPHARYNGEAL CARCINOMA (NPC) CELLS*****Hong May Gan<sup>1</sup>, Chee-Onn Leong<sup>1,2</sup>****<sup>1</sup>School of Pharmacy, International Medical University, 57000 Kuala Lumpur, Malaysia**<sup>2</sup>Centre for Cancer and Stem Cell Research, Institute for Research, Development and Innovation (IRDI), International Medical University, 57000 Kuala Lumpur, Malaysia*

High density of intratumoral cytotoxic T cells (CTL) in NPC patients was correlated with improved overall survival significantly. However, studies showed that tumor-intrinsic signaling pathways cause tumor resistance to CTL-mediated cytotoxicity. Despite recent advances in the management of NPC, novel therapy targeting CTL-resistant NPC cells has yet to be discovered. Parthenolide which has been shown to inhibit pro-survival signaling pathways, may reverse the tumor resistance to CTLs. Therefore, this study focused on investigating the cytotoxic effects of parthenolide against CTL-resistant NPC cells.

C666-1 cell line, an Epstein-Barr virus (EBV)-positive NPC cell line was employed in this study. From the transcriptomic data, the differentially expressed genes (DEGs) between the parental and the CTL-resistant NPC cells were determined. The Reactome pathway analysis was used to identify the highly enriched pathways in CTL-resistant NPC cells. Candidate drugs that could reverse the gene signatures associated with CTL-resistant NPC cells were identified through Connectivity Map computational drug repositioning algorithm. In the present study, the effects of parthenolide alone and cisplatin alone were tested on the parental cells and the CTL-resistant cells. The methyl thiazolyl tetrazolium (MTT) assay was used to analyse cell viability after drug treatment.

Seventy up-regulated genes and 302 down-regulated genes were identified in CTL-resistant NPC cells. The Reactome pathway analysis of DEGs revealed that they are involved in chemokine receptors binding, interleukin-10, interleukin-4 and interleukin-13 signaling, and heat shock factor 1-dependent transactivation. The connectivity map analysis showed that parthenolide with a connectivity score of -93.8, could reverse the gene signatures associated with CTL-resistant NPC cells. Parthenolide exerted dose-dependent cytotoxic effects against both parental and CTL-resistant cells without significant difference. CTL-resistant cells were significantly more sensitive than parental cells to cisplatin. Hence, these findings suggest that parthenolide could be a novel therapeutic agent for CTL-resistant NPC.

**LIGHTNING TALKS • DRUG DISCOVERY AND DEVELOPMENT****[LTD4]****NATURAL COMPOUNDS IN SELECTED CHINESE HERBAL MEDICINE AGAINST PROTEIN TARGETS IN SARS-COV-2: A MOLECULAR DOCKING STUDY**

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Since SARS-COV-2 infection has been declared as a pandemic and public health emergency in early 2020, no effective treatment has been proven against SARS-COV-2. As there is an urgent need to discover potential drugs towards COVID-19, we aimed to identify potential natural compounds in several herbal medicines used in Chinese medicine to manage COVID-19, that can potentially inhibit the target proteins which are crucial for the survival of the virus via a molecular docking study.

Several Chinese medicine herbs with possible antiviral properties and uses in treating COVID-19 infections have been identified based on previous literature. The compounds in each herb were selected after druggability criteria such as Lipinski's Rule of 5 have been applied. A molecular docking analysis was done using Autodock Tools 4.2 to identify the possible compounds that could inhibit the target proteins of SARS-COV-2 based on the lowest binding energy calculated.

Based on our molecular docking analysis, kaempferol had the lowest binding energy (-8.4kcal/mol) towards 3-Chymotrypsin-like (3CL) protease among the compounds in *Ephedra sinica*. Naringenin also had the lowest binding energy (-7.1kcal/mol) among the compounds in *Ephedra sinica* towards non-structural protein (nsp) 13 helicase.

From this study, kaempferol has the potential to inhibit 3CL protease, which is the main protease in SARS-COV-2, while Naringenin has the potential to inhibit nsp 13 helicase, in which inhibition of these two proteins could inhibit the replication process of SARS-COV-2. With these findings, further *in vitro* and *in vivo* studies can be done to further explore the ability of these two compounds as potential treatment for COVID-19.

**LIGHTNING TALKS • DRUG DISCOVERY AND DEVELOPMENT****[LTD5]****CANCER GENOMIC DATABASES ANALYSIS OF IKK $\alpha$  AS POTENTIAL TARGET FOR COLORECTAL CANCER*****Ka-Yann Kok<sup>1</sup>, Chee Onn Leong<sup>2</sup>, Ling Wei Hii<sup>1</sup>, Wei Meng Lim<sup>1</sup>****<sup>1</sup>School of Pharmacy, International Medical University, 57000, Bukit Jalil, Kuala Lumpur**<sup>2</sup>Institute For Research, Development & Innovation, International Medical University, 57000, Bukit Jalil, Kuala Lumpur*

Colorectal cancer is a common and lethal malignancy. Altered IKK $\alpha$  was depicted to be involved in cancer initiation and progression. The exact role of IKK $\alpha$  in colorectal cancer has not been fully defined. In this study, IKK $\alpha$  is analysed as a potential target in colorectal cancer through cancer genomic databases. A pan-cancer and cancer-specific analysis on *CHUK* gene alteration was done using cBioPortal. Differential mRNA expression analysis of *CHUK* gene was performed by utilising mRNA-seq data from Broad Genome Data Analysis Centre Firehose. The association of *CHUK* gene expression level with survival outcomes and tumour clinicopathological parameters of colorectal cancer was also investigated through cBioPortal. *CHUK* gene alteration was an infrequent driving mutation among various cancer types. Aberrant IKK $\alpha$  exerts pro-tumorigenic effects and is a poor prognostic marker in colorectal cancer. Downregulation of *CHUK* gene was discovered in colorectal tumours compared to adjacent normal tissues. There was an insignificant correlation between *CHUK* mRNA expression levels and survival outcomes, but a significant correlation with certain clinical attributes. Certain clinicopathological parameters were found to have correlation with both overexpressed and under-expressed IKK $\alpha$ . The study also identified significant genes such as *CXCL5*, *CXCL8*, *LY6G6D*, *NOTUM*, *GADPH*, *EEF2*, *CTNNB1* and *RICTOR* which were associated with colorectal cancer. The findings suggested that IKK $\alpha$  may be a novel therapeutic target in colorectal cancer, but validation work is required to confirm the findings.