8th RCMM

REGIONAL CONFERENCE ON MOLECULAR MEDICINE

In Conjunction with

4th National Conference for Cancer Research

ABSTRACT BOOK

UMBI
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in Conjunction with 4th National Conference for Cancer Research 2018
19-20th September 2018, Auditorium UMBI, Kuala Lumpur**

BoNT/X: A Tool to Study Intracellular Trafficking and Membrane Fusion

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ABSTRACT

Background: Botulinum neurotoxins (BoNTs) are a family of bacterial toxins classified as one of the most lethal toxin substances for humans. Despite this, there is an ever-growing list of medical conditions where the toxin has been successfully used as a mode of treatment. These toxins are taken up by neurons and specifically cleave SNAREs such as STX1, SNAP25 and VAMPs 1-3 thus blocking vesicle fusion and inhibits neurotransmitter release. SNAREs are core components of the intracellular machinery required for vesicle fusion. Their role in synaptic vesicle fusion is very well defined, in part because their function can be manipulated by Botulinum and Tetanus toxins. Very recently, a novel BoNT serotype has been identified, BoNT/X which is capable of cleaving a broader range of SNAREs (VAMPs 1-5 and Ykt6). **Methods:** To study the BoNT/X effect in intracellular transport, we fused the BoNT/X light chain sequence to a fluorescence reporter protein and transiently transfected non-neuronal cells. Analysis was performed using immunofluorescence microscopy and flow cytometry. **Results:** Our data indicates that BoNT/X cleaves an extended range of R-SNAREs. As a result of this, we have also observed that there is considerable disruption in the components of different transport routes involving the entire trafficking pathway to the plasma membrane. Functionally, the toxin perturbs endocytosis as it inhibits recycling of transferrin receptors to the cell surface. We can also demonstrate that the toxin disrupts constitutive secretion in our flow cytometry-based secretion assay models. **Conclusion:** The effects of the extensive SNARE-cleaving activity of BoNT/X on intracellular trafficking and transport needs to be further evaluated. We are currently investigating whether we can manipulate the expression of the toxin into an entity that can be controlled and regulated.

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Metabolomic Profiles of Different Stages of Colorectal Cancer

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ABSTRACT

Background: Improvement in the prognosis of colorectal cancer (CRC) involved early diagnosis and accurate staging of this disease. However, the molecular changes involved in the progression of this cancer are not well understood. In this study, global metabolomics profiling was performed on cell lines of different stages (Duke's A, B, C and D) in order to identify differentiating metabolites as well as unravel the pathophysiology involved in its progression. **Methods:** Cells were lyses and the extract was analysed using LC/MS QTOF 6250 Agilent. The metabolites were then determined using METLIN database. **Results:** The levels of 26 metabolites were significantly altered between the different stages of CRC cell lines. These metabolites include (Z)-13-Oxo-9-octadecenoic acid, 1,2,4-nonadecanetriol, 2-methylbutyroylcarnitine, acetylcarnitine, armillaripin, flavin adenine dinucleotide (FAD), flavine mononucleotide (FMN), glucose 6-phosphate, hexadecanoic acid, l-lactic acid, l-leucine, l-methionine, l-phenylalanine, l-tryptophan, lumichrome, lysoPE(0:0/16:0), lysoPE(0:0/16:1(9Z)), lysoPE(0:0/20:4(5Z,8Z,11Z,14Z)), lysoPE(0:0/20:5(5Z,8Z,11Z,14Z,17Z)), lysoPE(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/0:0), N,N'-Bis (gamma-glutamyl) cystine, pantothenic acid, phytosphingosine, pipericine, riboflavin, and tetradecanoylcarnitine. By using metaboanalyst 3.5 software, PLS-DA scores plot was able to discriminate the CRC cells from different stages. The highest VIP scores identified by PLS-DA was l-methionine. The pathway analysis showed metabolism of riboflavin as the most perturbed. Deficiency of methionine, and riboflavin may influence carcinogenesis due to their roles in the one-carbon metabolism pathway which is critical for DNA synthesis, methylation and repair. **Conclusion:** This study highlights the metabolites changes and the pathways affected at different stages of CRC and the potential biomarkers that can be used for staging of CRC.

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Gene-environment interaction in chronic kidney disease progression among Malaysians with type 2 diabetes mellitus

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ABSTRACT

Background: The study of gene-environment interaction may lead to a better understanding of biological and pathological mechanisms that contribute to chronic kidney disease (CKD) progression among type 2 diabetes mellitus (T2DM) patients. **Methods**: A total of 300 T2DM Malaysians from The Malaysian Cohort project were enrolled in a retrospective cohort study during recruitment (2008-2013) and follow-up phase until 2015. The endpoint was the occurrence of a renal event defined as the progression to higher stage of CKD. Thirty-two variants from 12 different genes were genotyped using Agena Mass Spectrometry. Predictors for disease progression were estimated using multiple Poisson regression. The adjusted predictive probability (APP) of disease progression was estimated from the generated gene-environment interaction. **Results:** During the study [mean follow up: 4.78(0.73) years], 62.7% patients progressed to higher CKD stage. Analysis showed that patients with *KCNQ1* rs2283228 (A/C) CC genotype and being female were almost two times at risk for disease progression (aRR: 1.78, 95%CI 1.20,2.64, p = 0.004 and aRR1.74, 95%CI 1.30,2.34, p < 0.001 respectively). Body mass index (BMI) measurement indicated that overweight patients were 4.5 times at risk (aRR: 4.54, 95%CI 1.43,14.46, p = 0.010) and obese patients were almost four times at risk (aRR: 3.84, 95%CI 1.21,12.15, p value = 0.022) for CKD progression. The APP of disease progression was higher for female than for male across *KCNQ1* rs2283228 genotype level. The probability of progression was also higher in overweight and obese patients compared to patients with normal BMI in all genotypes level. The probability of progression increased with higher number of C allele (CC>CA>AA). **Conclusion:** The *KCNQ1* rs2283228 CC genotype individually and in interaction with sex and BMI may modify the probability for CKD progression among T2DM patients. Further studies on gene–environment interaction is needed to obtain unequivocal conclusions that are generalisable to the general Malaysian population.

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Expression of Human Epidermal Growth Factor Receptor (HER) 4 isoforms and its localization in primary Herceptin-resistance breast cancer cell lines

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ABSTRACT

Breast cancer is the most common female malignancy worldwide. Overexpression of HER2 was observed in 15-20% of breast cancer and was associated with aggressive behavior. HER4 belongs to the human epidermal growth factor receptor of tyrosine kinase family which also includes EGFR, HER2 and HER3. In contrast to other members, the role of HER4 is uncertain where some reports suggest a tumor suppressive function while other suggests an oncogenic function. The conflicting role of HER4 in breast cancer is due to the presence of different HER4 isoforms and cellular localization. In addition, others also report involvement of HER4 in mediating resistance to Herceptin, a monoclonal antibody against HER2 receptor. However previous reports did not involve study in a panel of primary Herceptin-resistance breast cancer. In this study, we investigate the expression of HER4 isoforms and its localization in HER2 negative cell lines, MCF-7 and MDA-MB 231. The expression of different HER4 isoforms (CYT-1, CYT-2, JM-a and JM-b) was determined by RT-PCR while nuclear and cytoplasmic localization of HER4 was determined by western blot. In MDA-MB 231, both CYT and JM isoforms were expressed with the most highly expressed isoform is CYT-1. Meanwhile in MCF-7, expression of CYT-1 is negative and expression of CYT-2 is lower compared to JM isoforms. The nuclear and cytoplasmic protein extracted from MCF-7 shows higher expression compared to nuclear and cytoplasmic protein extracted from MDA-MB 231. From the results, even both cell lines are HER2 negative the expression and localization of HER4 is different.

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Identification of *Enterocytozoon bieneusi* proteins from serum of HIV patients by genomic and shotgun proteomic approach followed by bioinformatic analysis

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ABSTRACT

The microsporidian *Enterocytozoon bieneusi* (*E. bieneusi*) is a unicellular obligate intracellular parasite considered as an emerging opportunistic human pathogen and cause severe disease in immunocompromised individuals. This study aims to identify *E. bieneusi* proteins from serum of HIV patients via molecular methods. PCR analysis was performed to detect circulating *E. bieneusi* DNA in 100 blood specimens of HIV patients. Out of 100, 7 were confirmed positive. A gel-free shotgun proteomics analysis was then used to analysed positive *E. bieneusi* serum samples following the removal of albumin and IgG serum proteins. Serum was concentrated and mass spectrometry analysis was employed, enabling the detection of significant *E. bieneusi* proteins i.e. uncharacterized protein (B7XJ00), DNA topoisomerase 2 (B7XIW3), and actin (B7XHF2). Then, B7XJ00 protein was further analysed using bioinformatics tools to characterize its structure and the function. This study demonstrates that blood is a suitable clinical specimen for detection of *E. bieneusi* circulating DNA in disseminated cases. In addition, the shotgun mass spectrometry analysis results may provide possible serum biomarker candidates for clinical monitoring thus could serve as the basis for further proteomic investigation for human microsporidiosis. The diagnostic performance of these markers should be addressed prospectively.

Keywords: *E. bieneusi*, HIV, serum, shotgun proteomic, circulating DNA, microsporidiosis

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Mapping of Gut Microbiome Secretome in Colorectal Cancer

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ABSTRACT

The human gut is home to trillions of gut flora that thrive in delicate balance, which has helped maintain host's gut homeostasis and mutually benefited both parties tremendously. However, a drastic perturbation of microbial composition has hampered gut homeostasis initiating tumour microenvironment for development of colorectal cancer (CRC). The objective of this study was to profile secreted proteins from CRC and controls with healthy colon morphology by using mass spectrometry technology. Stool samples from 26 CRC and 20 controls were collected, homogenized and filtered prior to protein extraction and analysis. Samples were subjected for in-solution digestion, followed by protein identification and quantification. Bioinformatics tools such as SPSS, MaxQuant, DAVID and String were used for statistical analysis, data visualization, functional annotations and prediction of protein interactions and pathways. We identified more human origin proteins in CRC as compared to control & inversely for proteins from microbial origin. The best prediction model was built upon the combination of human Huntingtin & RNA exonuclease 5 proteins. The model was sensitive but not specific in discriminating control from CRC. The identified human exclusive proteins for CRC were mostly mapped to protein binding function and the top annotated KEGG pathway for human CRC-exclusive proteins was Hypoxia-inducible factor-1 (HIF-1). In addition, yeast proteins were topping the microbial CRC-exclusive proteins list, with the predicted protein interactions mapped to DNA repair, transcription regulation & ATP binding. In conclusion, gut flora and human colon released abundance of microbial proteins to the external environment possibly mediating various host-microbial reactions and responses in CRC.

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Leptin Enhances MNNG-Induced Tumorigenesis in the Stomach of Male Sprague-Dawley Rats

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ABSTRACT

Background: Obese people are at a higher risk of developing gastric cancer, yet its association with the augmented plasma leptin concentration in obese people is unknown. Leptin enhances the proliferation of gastric cancer cells *in vitro*, however its impact on tumour formation *in vivo* has not been examined. **Objectives:** This study therefore investigated the impact of leptin in a rat model of N-Methyl-N′-Nitro-N-Nitrosoguanidine (MNNG)-induced gastric adenocarcinoma. **Methods:** Male, Sprague-Dawley rats, aged six weeks, were divided into Group 1 (control); Group 2 (24 mg/kg/day of MNNG in drinking water); Group 3 (intraperitoneal injection of 60 µg/kg/day of leptin); Group 4 (MNNG and leptin) with 8 rats per group. After 40 weeks of treatment, rats were euthanized and stomachs were collected for histopathology, microarray analysis, and RT-qPCR. Data were analysed using Fisher's exact test and one-way ANOVA. **Results:** Gastric hyperplasia was observed in 50 % of MNNG-treated stomachs ($p<0.05$), with no changes in gene expression. Leptin-treated stomachs showed hyperplasia (12.5 %) and dysplasia (12.5 %) and upregulated expression of *Nupr1, Ybx1* (transcription factors), *Tmem134, Ptma* (oncogenes), *Eef1a1, Eif4g2* (translation factors), *Reep5* (cell proliferation), *Tmed2* (vesicular trafficking), and *Rab7a* (membrane trafficking) genes. Microscopically, 75 % of MNNG+leptin-treated stomachs showed gastric changes including hyperplasia, hypertrophy, dysplasia, and adenocarcinoma ($p<0.01$). Genes upregulated include olfactory receptors (signal transduction), *Hey2* (transcription factor), *Lcn11* (cell proliferation), microRNAs, and *Tmed2* (vesicular trafficking). **Conclusion:** It appears that leptin treatment significantly enhances MNNG-induced hyperplasia, hypertrophy, dysplasia, and adenocarcinoma in stomach of male Sprague-Dawley rats. These findings suggest leptin's role as both an inducing and contributing factor towards the increased prevalence of gastric cancer amongst obese people.

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Immunophenotyping of gastric cancers and non-gastric cancers using a cluster of differentiation (CD) antibody microarray

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ABSTRACT

Background and Aims: Gastric cancer develops through a cascade from mild to severe gastric diseases. Host immune response is one of the factors that play a role in the development of gastric cancer. Extensive immunophenotype of gastric cancer can be disclosed by using antibody microarray technique that profiles more than 100 CD antigens in a single assay. In this study, we used DotScan™ antibody microarray to determine CD antigen expression profiles for patients with various digestive diseases and to look for surface antigen disease-signatures. **Methods:** Blood samples from patients with various digestive diseases and gastric cancer were taken and processed for leukocytes isolation using Histopaque density gradient centrifugation. Leukocytes were captured onto DotScan™ slides and cell binding densities were analyzed using DotReader™. **Results:** Different groups of disease were found to be characterized by differentially expressed specific CD antigens. Compared to normal healthy controls, two CD antigens (CD22 and CD23) show differentially expression in gastritis, 10 CD antigens (CD11b, CD14, CD32, CD42a, CD45, CD49d, CD71 and lambda antibodies) in duodenal ulcer, 17 CDs in gastric and duodenal ulcer and 4 CDs (CD29, CD52, CD49f and CD182) in gastric cancer. CD antigens involve in T-cell functions and proinflammatory cytokines had reduced expression in gastric cancer. **Conclusions:** These results demonstrate specific immunophenotype of CD antigens for patients with various digestive diseases and identification of differential expressed surface antigens may have clinical significance for diagnostic and therapeutic purposes.

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Proteomics Analysis of Protein-Proteins Interactions

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ABSTRACT

Proteins are biomolecules that play important roles in diverse biological processes such as signal transduction, development and transport. Each protein possesses unique physico-chemical properties such as the order of amino acid sequence, 3D structure and post-translational modifications, which determine its biochemical functions. Another interesting property of protein is their abililty to interact with other proteins to form protein complexes that can either be stable or transient. By forming protein complexes, the functional repertoire of proteins can be greatly expanded, despite only ~20,000 protein coding genes are encoded by the human genome, for instance. To identify the individual components of these protein complexes, affinity purification or immunoprecipitation are often applied whereby an epitope-tagged protein or an antibody targeting a known component are used to “pull down” or enrich the remaining whole complex. Individual members are then identified one by one using Western blot. However, currently Western blot has increasingly been replaced by mass spectrometry and the members of the protein complex can be identified in one experiment. These methods are collectively named the Affinity Purification – Mass Spectrometry (AP-MS) approach. Generally, AP-MS method comprises four essential steps i.e. (i) biological sample preparation (ii) protein purification (iii) MS analysis and (iv) data and bioinformatic analysis. In this presentation, I will discuss the importance and precautions for each step in setting up an in-house pipeline for AP-MS experiments.

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The treatment of epigenetic drugs, Trichostatin A and Zebularine, followed by Tumor Necrosis Factor-related Apoptosis-inducing Ligand (TRAIL) halts cell cycle progression in the triple-negative breast adenocarcinoma cells, MDA-MB-231

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ABSTRACT

Breast cancer is the leading killer among women. Breast cancer is urgently in need of a treatment option which eliminates cancerous cells leaving untransformed cells mostly unharmed. Along this vein, Tumour Necrosis Factor-related Apoptosis-inducing Ligand (TRAIL) is worth being researched on for its anti-cancer properties. Nonetheless, most cancers including breast cancer are resistant towards TRAIL-induced apoptosis. Therefore, this research aims to answer whether TRAIL resistance can be alleviated by first sensitizing human breast adenicarcinoma MDA-MB-231 cells with the epigenetic drugs, Trichostatin A (TSA) and Zebularine (Zeb) prior to TRAIL treatment (TZT). The MTT [3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide] cell viability assay was used to assess the extent of treatment-induced inhibition of cell viability. The MTT cell viability data showed that the TZT treatment has reduced the cell viability significantly ($P<0.05$) in E-cadherin-re-expressed MDA-MB-231cells (48%). Besides, by using the ethanol fixing and propidium iodide staining cell cycle analysis, TZT treatment has induced significantly the highest G_0/G_1 arrest (59.6%) among all other treatment groups in MDA-MB-231. RT-PCR was used to assess the mRNA expression changes of the pro-survival genes proliferating cell nuclear antigen (PCNA) and cyclin-dependent kinase 2 (CDK2). The results show that TZT treatment has downregulated the mRNA expression of PCNA and CDK2 in MDA-MB-231 in comparison with TRAIL and TSA and Zeb (TZ) combined treatment, respectively. In conclusion, further research on the sensitization of breast cancer cells towards TRAIL killing by epigenetic drugs is warranted.

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Microsatellite D19S884 in Malay Women with Polycystic Ovary Syndrome

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS), is the most prevalent endocrine disorder in women. A PCOS susceptibility gene (fibrillin 3 gene, FBN3) had been mapped to chromosome 19p13.2 with the strongest association being with the dinucleotide repeat microsatellite genetic marker, D19S884. Whereas the PCOS susceptibility locus D19S884 allele 8 (A8) has been replicated in Caucasian studies, A7 seems to be the most prevalent among Han Chinese PCOS subjects. Since the presence of D19S884 is more likely to confer insulin resistance, β-cell and other metabolic dysfunctions, it is of clinical importance to be able to detect this in a local Malay population. **Methods**: DNA was extracted from blood obtained from PCOS (n=27) and non PCOS patients (n=20). DNA microsatellites were amplified by PCR using a pair of specific primers tagged with fluorescence to yield products of 160-200 base pair in length. Alleles were separated on 4% low-melting agarose gels electrophoresis to preliminarily confirm the success of PCR. It was followed by fragment analysis using the capillary gel electrophoresis. **Results**: Eleven different alleles ranging between 12-21 repeats were identified and the most frequent allele observed was of 18 repeats (A9). The highest allele frequency noted was A9 (30%), followed by A6 (17%) and A5 (16%). The distributions of D19S884 genotypes between PCOS patients and control women were not significantly different. Although frequency of A9 in PCOS is more than control, the difference is not significant (P-value = 0.6221). No significant difference was observed in the insulin resistance status (p=0.736). **Conclusion**: Despite insignificant results due to small sample size, findings in this study provide new genetic information for Malay PCOS patients. More data is needed in future to understand the pathophysiology of this condition, which D19S884 may be a potential molecular marker for PCOS risk in our population.

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Assessment of 25 Trace Element Levels in Patients with Colorectal Cancer: A Case Control Study in UKM Medical Centre

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ABSTRACT

Background: Trace elements' metabolism has been reported to possess specific roles in the pathogenesis of colorectal cancer (CRC). The balance between essential and toxic elements is thought to be crucial in impeding the development of CRC. To date, limited studies were conducted to evaluate from this aspect. This study aims to determine the level and distribution of 25 trace elements in CRC patients. **Methods:** A case-control study was conducted among 102 CRC patients and 102 controls. The blood serum was acid-digested and the levels of 25 trace elements (Li, Be, Mg, Al, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Rb, Sr, Ag, Cd, Cs, Ba, Hg, TI, Pb, U) were determined simultaneously using an inductive coupled plasma-mass spectroscopy (ICP-MS). Statistical analyses were performed by using independent t-test, Mann-Whitney, Spearman's correlation coefficient, principal component analysis (PCA) and cluster analysis (CA). **Results:** Differential levels and distribution pattern of trace elements were observed between CRC and control. The study evidenced higher concentration levels for 12 trace elements (Li, Be, Al, Co, Cu, As, Cd, Rb, Ba, Hg, TI, Pb) with lower concentration for Zn and Se found in the serum of CRC patients ($p < 0.05$). We also observed a higher number of trace elements correlated to each other in the CRC patients in comparison to the controls. The PCA of the 14 significant trace elements was able to distinguish the CRC patients from the controls. Moreover, the CA indicated that three essential elements (Cu, Zn, Se) were not clustered closely in the CRC patients as compared to controls. **Conclusion:** These findings indicate that the level and distribution of trace elements in CRC patients and controls are significantly divergent. The variation observed may suggest a strong involvement of these elements in the molecular mechanism of CRC. Further evaluation on the biologic role of these trace elements in the development of CRC is warranted.

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The anti-hyperglycemic and pro-fertility effect of combination *Gynura procumbens* and Kelulut honey in diabetic-induced male rats

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ABSTRACT

Exploration of natural product combinations could be an alternative approach for developing nutritional supplements. *Gynura procumbens* (GP) and Kelulut honey (KH) are two natural products that are well known for traditional treatment of diabetes mellitus (DM) and male fertility problem. Combination of potent anti-hyperglycemic effect of GP and pro-fertility effect of KH is expected to produce an optimum antidiabetic and pro-fertility effect in diabetic subjects. Hence, the aim of this study was to evaluate the synergistic effects of the combination in diabetic-induced male rats. Rats were randomly divided into six groups; three control groups (normal, positive and negative) and three treated groups with three different treatments (GP 150 mg/kg BW, KH 300 mg/kg BW and combination of GP: KH (150: 300 mg/kg BW)). Diabetic condition was induced with a single dose of 50 mg/kg BW streptozotocin prior to the treatment. Oral administration of the treatments for 14 consecutive days significantly decreased the fasting blood glucose level to the normal blood glucose level compared to negative controls. The administration of the GP-KH combination significantly improved fertility in terms of sperm quality. The increment of libido, significant elevation of testosterone level and improved testes histology were fairly displayed in the treated groups compared to the negative control group. Combination of GP-KH also revealed several sperm protein candidates that play important roles in fertility. In conclusion, combination of GP-KH has potential to be developed as an anti-hyperglycemic, pro-fertility and libido agent for diabetic patients.

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Landscape of copy number alterations and allelic imbalances in HPV16-positive cervical carcinomas

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ABSTRACT

Somatic copy number alterations (CNAs) and allelic imbalances (AIs) are common features of solid tumors. In cervical cancer, the loci at which these molecular events frequently occur, as well as the genes involved, remained poorly understood. In this study, we aimed to characterize the genome-wide CNAs and AIs in cervical cancer, focusing on carcinomas caused by HPV16 (i.e. the most common and oncogenic human papillomavirus known in cervical cancer). Genomic DNA was isolated from the matched cancerous and adjacent non-cancerous cervical tissues from 20 histopathologically-confirmed patients who were tested positive for HPV16. Characterization of CNAs and AIs was then performed by using Affymetrix CytoScan HD Array and analyzed with Chromosome Analysis Suite (ChAS) software. The most common recurrent loci at which these molecular events occurred were identified by manual counting. Gene annotation was then performed based on NetAffx Genomic Annotation file NA33.1 (Hg19). It was found that somatic copy number gains occurred most frequently at 1p36.32 (80% of the samples), 8q24.3 (75.0%) and 10q26.3 (65.0%) loci. These three loci contained 37, 114 and 41 genes respectively. On the other hand, the loci at which somatic copy number losses were commonly observed were 11p11.12 (75.0%), 11p15.4 (55.0%) and 3p11.1 (55.0%), which respectively contained 45, 172 and 3 genes. Besides, it was also found that almost all of the samples analyzed (19/20; 95.0%) had AIs at Xq11.1 locus, at a region which contained 126 genes. This was followed by Xp11.23 (60.0%; 164 genes) and Xq22.3 (55.0%; 409 genes). In conclusion, this study has successfully identified a few genomic loci at which tumor-specific CNAs and AIs were commonly observed in cervical cancer.

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Detection and Characterization of *Leptospira* spp. in Semi-captive Orangutans and Rangers/zookeepers in Bukit Merah Orangutan Island (BMOUI) and Zoo Taiping, Perak

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ABSTRACT

Leptospirosis is a bacterial disease caused by spirochetes in the family Leptospiraceae, genus *Leptospira* that may infect both human and animals. The study was carried out to determine the exposure of leptospirosis that circulates among orangutans, rangers/zookeepers and rodents in Bukit Merah Orangutan Island (BMOUI) and Zoo Taiping, Perak. Blood samples were obtained to determine the presence of antibodies against *Leptospira* through the microscopic agglutination test (MAT) using 21 serovars of *Leptospira* commonly found in Malaysia as antigens. It was observed that *Rattus exulans* (1/10) (10.0%), *Rattus rattus* (1/5) (20.0%), *Niniventer fulvescens* (1/1) (100.0%), *Callosciurus notatus* (0/6) (0.0%), *Tupaia tana* (1/1) (100.0%), *Pongo pygmaeus* (5/10) (50.0%) and rangers (8/18) (44.4%) from BMOUI while *Rattus rattus* (0/19) (0.0%), *Rattus exulans* (1/2) (50.0%) and zookeepers (2/5) (40.0%) from Zoo Taiping were positive for leptospiral antibodies. Among the positive cases, most samples from both areas reacted with serovar Lepto 175. Detection of leptospires through PCR has been carried out on positive culture samples from environment using 16S rRNA primers. Based on BLAST results of 16S rRNA sequences, out of 14 positive environmental cultures from BMOUI, two were determined as pathogenic isolates while four isolates shared identical genetic profiles with intermediate leptospires (*L. idonii and L. wolfii*) and eight isolates with saprophytic species (*L. yanagawae and L. meyeri*). As for Zoo Taiping, all 15 positive environmental cultures were identified as non-pathogenic strains which shared identical genetic profiles with *L. yanagawae and L. meyeri*. Characterization of leptospires through multi-locus sequence typing (MLST) was conducted on pathogenic samples based on a published scheme targeting seven loci. Pathogenic isolate labelled 'Soil2' from BMOUI environmental sample gave exact but partial MLST allelic profiles making *L. interrogans* serovar Lai Langkawi (ST: 236) as the nearest match to the sample. Another pathogenic isolate labelled as 'BJ3 soil' from BMOUI environmental sample was given new allelic profiles which led to a new assigned ST number 262 (unknown species). Detection and characterization of leptospires through PCR has also been carried out on tissue/ urine samples from rodents and orangutans using flaB and rrs2 primers respectively. Based on phylogenetic tree constructed from aligned sequences of rrs2 gene, leptospires in one urine sample from BMOUI rodent was shown to be closely related with *L. wolfii* strain UPM-Jeli 3 while those that were detected in one urine sample from BMOUI orangutan seemed to be closely related with *L. wolfii* strain UPM K. Bharu. Leptospires found in urines of two orangutans from Zoo Taiping were shown to be

closely related with *L. wolfii* strain UPM K. Bharu and *L. kirschneri* strain MORU MO6. Based on survey conducted on workers from BMOUI and Zoo Taiping, there were no significant association between seroprevalence of leptospiral antibodies with age ($p = 0.853$), sex ($p = 0.801$), ethnicity ($p = 0.916$), educational level ($p = 0.537$) and working experience ($p = 0.853$). In terms of risks factors, there were no significant association between seroprevalence of leptospiral antibodies with working hours ($p = 0.269$), smoking ($p = 0.528$), crossing rivers/pools/stagnant water while working ($p = 0.525$), wearing full personal protective equipment (PPE) ($p = 0.890$), exposures to rodents in orangutan/primate sections ($p = 1.000$) and exposures to rodents in working areas ($p = 1.000$). To conclude, this study has provided epidemiological and clinical data on leptospirosis in BMOUI and Zoo Taiping which can be important for improving strategies in prevention and control of the disease thus helping in conservation of the orangutans.

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PASD1, a Potential Immunotherapeutic Peptide in Colorectal Cancer (CRC)

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ABSTRACT

Despite the advances in conventional therapies and preventive screening for colorectal cancer (CRC), a subpopulation of CRC patients still fail to attain long term remission or suffer from unwanted toxic side effects. The immunogenic cancer testis antigens (CTAs) with their widespread expression in a variety of cancers but highly restricted in normal tissues, except testis, represent an attractive approach to improve treatment options for CRC. PAS (Per ARNT Sim) domain containing 1(PASD1) is a CTA reported to be expressed mostly in hematopoietic malignancies but has limited expression in solid tumors. The aim of the present study was to investigate the expression of PASD1, CD-8 T immune responses and its cytokine profiles in CRC patients. PASD1 mRNA expression was determined via RT-PCR on paired tumor and normal tissue samples from 25 CRC patients. Tissue expression of PASD1 was assessed via immunohistochemistry (IHC) in another 23 CRC samples. Four immunogenic PASD1 peptides predicted to bind to major histocompatibility complex (MHC) Class 1 allele were identified using web-based algorithms. Peripheral blood mononuclear cells from CRC patients were used to investigate the immunogenicity of these HLA-A*2402 restricted peptides *in vitro* using IFN-y release ELISpot assay. The effects of effector CD8+ T-cells pulsed with PASD1 peptides against different cancer cells were detected in cytolytic and granzyme-B release ELISpot cytotoxicity assays. Cytokine profiles of the studied CRC patients were assessed. Gene and protein expression of PASD1 was detected in 20% and 21.3% of CRC samples respectively. PASD1(4), was shown to be selectively immunogenic in CRC patients. CD8-positive cytotoxic T cells from three patients raised against PASD1(4) were able to lyse HLA-A*2402 positive-SW480 cell line expressing endogenous PASD1 protein in all three effector/target ratios. The elevated cytokines: IFN-y, Granzyme A, Granzyme B and perforin were detected in all three CRC patients. CD8-positive CTL response to PASD1 protein in CRC patients were examined in our findings. These preliminary results show that PASD1 peptide is a probable immunogenic antigen and represents a potential target for peptide-based immunotherapy in CRC.

Keywords: PASD1, cancer testis antigen, HLA-A*2402, cytotoxic T-cell, colorectal cancer, immunotherapy

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Cytotoxic properties of the venoms and cytotoxins of Malaysian cobras, *Naja sumatrana* and *Naja kaouthia* on selected cancer cell lines

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ABSTRACT

Cancer is leading cause of death worldwide. The search for novel anticancer agents is important to ensure effective and target-specific therapies are available in cancer treatments. Cobra venoms, known for their cytotoxic effect, are a promising source of naturally occurring bioactive compounds with potential anticancer properties. Here we investigated the cytotoxic activities of the holovenoms and purified cytotoxins of two Malaysian cobras, *Naja sumatrana* (equatorial spitting cobra) and *Naja kaouthia* (monocled cobra) on three cancer cell lines, i.e., MCF-7 (breast), A549 (lung) and PC-3 (prostate). The venoms were milked from multiple cobras according to the species, and the cytotoxins were purified via sequential fractionation using ion-exchange chromatography, followed by C_{18} reverse-phase high-performance liquid chromatography (HPLC). The protein homogeneity was validated on sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and identified through liquid chromatography-tandem mass spectrometry (LCMS/MS). The half maximal inhibitory concentration (IC_{50}) of the holovenoms and cytotoxins across the three cell lines were obtained with MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. The IC_{50} of the holovenoms varied across the cell lines, with the most potent growth inhibitory effect observed on A549 (IC_{50} = 2–4 µg/ml) followed by PC-3 (IC_{50} = 4–7 µg/ml) and MCF-7 being with least potent (IC_{50} = 10-35 µg/ml). The purified cytotoxins of *N. sumatrana* and *N. kaouthia* showed, IC_{50} values approximately 3 times lower than the values of the holovenoms, indicating that the cobra cytotoxins are more potent in inhibiting cancer cell growth. These cytotoxins showed higher specificity against A549 and PC-3 (IC_{50} = 1–2 µg/ml) compared to MCF-7 (IC_{50} = 9–12 µg/ml). The findings show that the cytotoxins of Malaysian cobra venoms, have promising cytotoxic effects against the cancer cell lines. Further research is needed to explore the anticancer selectivity and the underlying mechanistic actions of these cytotoxins.

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Serum Metabolomics Profiling in the Identification of Biomarkers for Colorectal Cancer

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ABSTRACT

Background Late diagnosis of colorectal cancer (CRC) is often attributed to its lack of symptoms and the invasive techniques employed to confirm the condition. Less invasive screening tests are neither accurate nor specific for CRC. Therefore for better prognosis, a more accurate, specific and non-invasive test is needed. In this study, we performed global metabolomics on CRC serum samples compared to healthy individuals in order to identify metabolites that can differentiate the condition. **Methods** Blood from 50 healthy controls and 50 CRC patients were collected at Hospital UKM. The serum samples were deproteinised with acetonitrile and then analysed using liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOFMS, Agilent USA). The data were analysed using Mass Profiler Professional (Agilent, USA) software. **Results** The levels of acetylcarnitine and hypoxanthine showed significant differences between CRC patients and normal control. The altered levels of these metabolites were detected in 80% of CRC samples. Based on analysis of area under the curve, these metabolites showed high sensitivity and specificity as biomarkers. The alterations in these metabolites suggest perturbations of purine metabolism and fatty acid oxidation. **Conclusion** These results suggest the potential of these metabolites as biomarkers for detecting CRC.

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Clinacanthus nutans (Acanthaceae) induced macrophage-mediated antitumor response in nude mice

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ABSTRACT

Clinacanthus nutans (Acanthaceae), is a plant that traditionally used to treat inflammation related diseases and cancer. This study was aimed to investigate the in vivo antitumor properties of *C. nutans* ethanol and water extracts. Female nude mice were inoculated with 1 x 10^7 MDA-MB-231 cells on the right shoulder for evaluation of tumor progression in vivo. Following the formation of tumor to the size of ~100mm^3, the mice were randomly divided into 4 groups: Untreated control group, acetylsalicilic acid (ASA) treated group (positive control, 40 mg/kg), ethanol extract treated group (100 mg/kg), and water extract treated group (100 mg/kg). The treatment were given orally for 30 days. The tumor size was measured twice weekly with a digital caliper. Results showed that both *C. nutans* ethanol and water extract significantly inhibited the growth of tumor in nude mice model (p<0.05) as compared to the control group. Serum analysis showed that *C. nutans* extracts were able to significantly (p<0.05) reduced the expression of IFN-γ and IL-6 but not the IL-2, IL-1β, TNF-α and VEGF expression. Further investigation on the tumor sections showed that there were an increase of macrophage infiltration into the tumor sugggesting that *C. nutans* extracts promotes its antitumor properties via modulating the immune response. In conclusion, *C. nutans* extracts possesed antitumor activity in vivo by inhibiting the progression of tumor growth via macrophage-mediated antitumor response.

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Genetic Diversity in the E5, E7 and E7 Proteins of HPV-18 from Cervical Cancer patients in the West Sumatera and Riau Provinces, Indonesia

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ABSTRACT

Human papillomavirus (HPV) is cervical epithelial infectious agent. Epidemiology proved that one of the major cause of cervical cancer was HPV type 18. Whereas the proteins that give a high risk to cervical cancer case were E5, E6, and E7. Several studies stated the expression of E5, E6 and E7 protein can induced cervical cancer. The purpose of this studies were to find genetic diversity of *Human papillomavirus* proteins from patients with Cervical Cancer. DNA samples were isolated from cervical cancer tissues and amplified using MY9/11 and GP 5/6 primer pairs for HPV. HPV 18 were identified with specified primers and continued with primers for sequencing E5, E6 and E7 genes. Phylogenetic and sequences analysis was performed and sequences were compared to reference sequences HPV-18 (X05015) using Clustal-X. One hundred and forty seven tissues were colected and 62 samples were positif with HPV. Twenty-four samples were HPV 18. The mutations vary between E5, E6 and E7 genes. SNPs were 56% in E5, 44% in E6 and and 48% in E7. Most of SNPs were non-synonymous. The majority of the non-silent variations were located in sequences encoding alpha helix, beta sheet or surface loops, in particular in the immunodominant FG loop, and may influence the protein secondary structure and immune recognition.
Based on this research, we concluded that molecular diversity were found on E5, E6 and E6 genes HPV 18 and may influence the protein secondary structure and immune recognition.

Keywords : Cervical cancer, HPV 18, genes, molecular diversity, phylogeny

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The apoptotic effects of curcumin analogue DK1 towards colon adenocarcinoma cell line, HT29

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ABSTRACT

Curcuma longa, commonly known as turmeric, contains curcumin which is its main compound which has been reported to possess a wide variety of pharmacological activities such as anti-carcinogenic, anti-malarial, antioxidant, antibacterial, anti-mutagenic, anti-inflammatory and immunomodulatory effects. Even though it has many strong biological properties, curcumin lacks in its solubility and this affects its clinical efficacy altogether. DK1 is a curcumin analogue which has been found to possess selective cytotoxicity on breast cancer cells compared to normal breast cells, however, its effectiveness on colon cancer have yet to be validated. The main objective of this study is to investigate the apoptotic effects of DK1 towards human colon cancer cell line, HT29. The MTT assay was incorporated to determine the cytotoxic effect of DK1 towards the cells while flow cytometry analyses (Annexin V/FITC, cell cycle and JC-1) were executed to determine the mode of cell death. Finally, quantitative Real-Time PCR and proteome profiling were done to further investigate the mechanisms involved in the cells' apoptosis. Results showed DK1 inhibiting cell viability and proliferation in 48 hours with IC_{50} value of 7.57±1.69 µM which is much lower compared to curcumin with IC_{50} value of 20.2 ± 0.6 µM, showing its increased cytotoxicity towards HT29 cells. DK1 also caused cell cycle arrest with cell population of 23% at S phase and 28% cell accumulation at sub-G_0/G_1 phase. The flow cytometry analyses also showed that treatment of DK1 for 48 hours induced apoptosis in HT29 through intrinsic pathway. Quantitative Real-Time PCR showed significant up-regulation in the expression of caspase-3 and caspase-9 genes, while proteome profiling revealed up-regulation in pro-apoptotic proteins, Bax and cytochrome c. The outcome suggests that DK1 is a potential anti-cancer agent for colon cancer due to its anti-apoptotic attributes.

Keywords: colon adenocarcinoma, curcumin analogue DK1, mitochondria-dependent, apoptosis, *in vitro*.

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19-20th September 2018, Auditorium UMBI, Kuala Lumpur**

Differential Gene Expression Analysis of Pediatric AML Trios

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ABSTRACT

Acute myeloid leukemia (AML) is the second most common leukemia type among children, and nearly 50% of pediatric AML patients will relapse and succumb to the disease. Clinically, relapsed AML patients respond poorly to standard chemotherapy regimens, therefore there is a need to investigate the genes involved in relapsed AML in order to personalise treatment and improve patients' survival via targeted therapy. Transcriptome sequencing (RNA-seq) was performed on trio (at diagnosis, remission and relapse) samples of three pediatric AML patients. The differential gene expressions in all three samples were analyzed via the edgeR method. The gene ontology and pathway analysis were performed using the KEGG and GO databases. Furthermore, the expression data for several selected genes were validated using real-time quantitative PCR in an additional 26 samples at diagnosis, 13 at remission and 7 relapse samples. The expression ratios were calculated using the ΔΔCT method after prior validation of the method for each target. We obtained three sets of differentially expressed genes (DEGs) for the three comparison groups, relapse vs diagnosis, relapse vs remission and diagnosis vs remission. The DEGs for the relapse vs diagnosis group were enriched in the cell cycle-related pathway. Meanwhile, the DEGs in the relapse vs remission were enriched in the ECM-receptor interaction pathway. Among the DEGs, ADGRL3, TOP2A and SEL1L2 were validated via qRT-PCR. The results were in concordance with the RNA-seq data. Since little is known about the molecular mechanisms underpinning relapsed AML, this study has allowed us to obtain a preliminary snapshot to understand the pattern of gene expression in relapsed pediatric AML. These early findings may be used to further comprehend the molecular pathways contributing towards relapse pediatric AML.

Keywords: pediatric AML, transcriptome, RNA-seq, relapse, differentially expressed genes

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Proteomics and neutralization of the venoms of Eastern Russell's viper (*Daboia siamensis*) from Thailand and Indonesia

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ABSTRACT

Envenomation by *Daboia siamensis*, the Eastern Russell's viper can lead to deranged affecting haemostasis and death. However, the venom compositions of *D.siamensis* from different geographical locales could be different, resulting in variable clinical presentation of envenomation and antivenom efficacy. The study investigated the protein profiles of *D.siamensis* venoms from Thailand and Indonesia with C_{18} reverse-phase high-performance liquid chromatography (RP-HPLC), sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and liquid chromatography-tandem mass spectrometry (LCMS/MS). Lethality and procoagulant activity of both venoms were assessed in mice and human citrated plasma respectively. The immunoreactivity of Thailand *D.siamensis* Monovalent Antivenom (DsMAV) and Indonesian trivalent Serum Anti Bisa Ular (SABU) were compared using an indirect enzyme-linked immunosorbent assay (ELISA), and the neutralization efficacy of DsMAV against both venoms was assessed. The venom proteomes of both *D. siamensis* were predominated with phospholipase A_2 (37-48%), snake venom serine protease (17-22%) and other hemotoxins at varying abundances. The venoms were highly lethal in mice (median lethal dose, LD_{50}= 0.22-0.34 µg/g) and procoagulant in plasma (minimum clotting dose, MCD= 0.004 µg/ml - 0.024µg/ml respectively, for Thai and Indonesian samples). In ELISA, DsMAV showed significantly higher immunoreactivity than SABU toward both venoms, indicating that the species-specific antivenom (DsMAV) was able to bind *D. siamensis* venom antigens more effectively. DsMAV showed comparable immunoreactivity toward both venoms, however, it neutralized the procoagulant effect of the Thailand *D.siamensis* venom with higher efficacy (n-ED= 7.48mg/g) compared to that of Indonesian venom (n-ED= 41.06mg/g), as the Thailand venom was less potent in procoagulant activity. The findings revealed geographical variation of *D.siamensis* venom from Thailand and Indonesia in terms of venom proteomes, LD_{50} values and the immunoreactivity as well as neutralization effect of antivenoms. Further research is needed to investigate the in-vivo antivenom efficacy.

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Differential gene expression of papillary thyroid carcinoma reveal important genes for lymph node metastasis

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ABSTRACT

Papillary thyroid carcinoma (PTC) is the most prevalent thyroid cancer. Here, we explored the differential expression of the transcriptional regulation programme in thyroid cancer. The main objectives of this study are to determine the genes involved in lymph node metastasis in papillary thyroid cancer. We employed a pipeline for RNA-seq analysis in PTC with and without lymph node metastasis at gene expression level. Expression profiling revealed changes in the PTC with lymph node negative (LNN) (33 genes at p-value < 0.05 and $\log_2$ fold change |1.0|) compared to the adjacent normal thyroid, whereas 69 genes in the PTC with lymph node metastasis (LNM) in the same comparison. We identified 31 significantly up-regulated genes in PTC LNM versus PTC LNN. Moreover, 35 genes were significantly down-regulated in PTC LNM compared to PTC LNN, 38 genes in PTC LNM compared to normal thyroid, 90 genes in PTC LNN compared to normal thyroid and 56 genes between normal thyroid tissues. The genes expressed at higher levels in PTC LNM compared to LNN included cell communication, energy pathway, and metabolism whereas ion transport, energy pathways, and regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism, all were downregulated. These findings can provide further evidence for the transport regulatory programme to govern the lymph node metastasis (LNM).

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The Role of Alpha-Giardin in Response to Drug Treatment in *Giardia Intestinalis*

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ABSTRACT

Giardiasis, which is caused by the intestinal protozoan parasite *Giardia intestinalis*, affects approximately 280 million people around the world. Giardiasis mainly affects school children from the lower socio-economic background, particularly those living in the rural parts of Malaysia. The prevalence of giardiasis in Malaysia has been reported to range from 1.4% to 11.1%. Oral ingestion of as few as ten cysts of *G. intestinalis* can cause infection in human which lead to complications such as severe diarrhea, dehydration and weight loss. There are several antigiardial drugs available for giardiasis treatment; however, issues such as drug resistance, reinfection and recurrence of symptoms have been highly reported. Thus, the finding for a novel potential drug targets is important to control the disease. In this study, we sought to examine the role of alpha-giardins in response to drug treatment in *G. intestinalis*. Our results showed that *G. intestinalis* were more susceptible to the action of Mebendazole (MBZ) with IC_{50} value of 0.06 µM when compared with Metronidazole (MTZ) of 9.177 µM. Trophozoites treated with high concentration of MBZ or MTZ showed significant reduction in viability. The release of reactive oxygen species was not detected in either MBZ or MTZ-treated *G. intestinalis*. We also found that *G. intestinalis* treated with 100 µM MBZ or MTZ showed significant upregulated expression of alpha-2 giardin ($p \leq 0.05$). In conclusion, these observations suggest that alpha-2 giardin could serve as a potential promising target for future drug design and vaccine development.

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Alteration of Gut Mycobiota in Colorectal Cancer: An Evidence from a Gut Microbiome Secretome Study

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ABSTRACT

Background: The importance of mycobiota in human gut health has gained recent interest as evidenced by the shift of the current probiotics paradigm from the use of bacteria to yeast. However, little is known about the role of these naturally occurring mycobiota in the gut microenvironment and their effects on the host, particularly in a chronic term such as colorectal cancer (CRC). Therefore, we aim to identify the secreted proteins released from the human gut mycobiota by assessing the secretome in the stool samples. **Methods:** Stool samples from 26 clinically-diagnosed patients with CRC and 20 non-CRC control individuals were collected, homogenized and filtered followed by protein extraction and profiling by quantitative label-free proteomics using Nano-Liquid Chromatography TripleTOF Mass Spectrometry. The mass spectra datasets were searched using MaxQuant against the fungi's Uniprot Fasta databases. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 22. Functional and integrative analyses of the identified proteins were performed using the Database for Annotation, Visualisation and Integrated Discovery (DAVID) and MetaboAnalyst 4.0 online tools, respectively. **Results:** We identified 589 proteins secreted by the gut mycobiota with 35 proteins specific to CRC. In contrast, 554 proteins were exclusive to the non-CRC controls and no common yeast protein was identified in both groups. Interestingly, the distribution of the secretome proteins identified from the yeast was skewed towards the control samples. We also observed great variation in the secretome of the yeast species in the studied individuals, regardless of the presence or absence of CRC or early- or late-stage CRC as revealed by discriminant and heat-map analyses. The predicted protein interactions for the top 20 of the identified yeast proteins were mapped to DNA repair, transcription regulation and ATP binding. **Conclusion:** The alteration of fungal proteins observed in CRC may suggest a modified micro-tumour environment for these fungi. This knowledge may be exploited for new therapeutic approaches for gut-related issues.

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Molecular Identification of Maggots Species in Forensic Entomology using Cytochrome Oxidase Subunits 1 - Preliminary Study

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ABSTRACT

Forensic entomology is a discipline that mainly uses insects collected in and around corpses to estimate the post-mortem interval (PMI) in medico criminal investigations. The conventional method to find out the species of maggots is usually through microscopy, however, this method has its limitation especially if the maggots come with incomplete morphology characteristics or too immature for comparison. To date, recent molecular studies had focused on cytochrome oxidase 1 gene (CO1) as the most common molecular markers for maggot's identification in forensic entomology. The aim of this study is to identify some important species in forensic entomology using conventional Polymerase Chain Reaction (PCR) to amplify the CO1 gene. Four preserved species of maggots which were taken from the Forensic Entomology Unit, PPUKM (*Sarcophaga* sp., *Synthesiomyia nudiseta*, *Chrysomya rufifacies* and *Chrysomya megacephala*) were used as samples. After DNA of the samples were extracted, all samples were subjected to PCR analysis and DNA sequencing analysis. Based on the result, 348bp of CO1 gene of all the samples can be amplified using the same set of primers. The species sequences analysis results showed that this gene gives enough information to identify *Ch. megacephala* and *Ch. rufifacies* while another two species had almost similar sequence with CO1 gene of *Hemipyrellia ligurriens.* This result will facilitate further research using molecular methods such as Loop-mediated Isothermal Amplification (LAMP) for a more precise, rapid and convenient tool to avoid time-consuming procedure for identification purposes.

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PASD1 expression in Lymphoma Patients at UKM Medical Centre (UKMMC)

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ABSTRACT

Background: Per ARNT Sim Domain containing Repressor 1 (PASD1) is one of the cancer testis antigens (CTAs) which have restricted expression in normal tissues but widespread expression in cancers. This makes PASD1 as an attractive immunotherapy target. Two *PASD1* transcripts have been identified namely *v1*, which encodes 639 aa N-terminus while *v2*, encodes a longer protein (773 aa) with a unique C-terminus. This study aims to investigate the expression of PASD1 in the lymphoma patients from UKM Medical Centre. **Method:** Formalin-fixed paraffin-embedded (FFPE) sections from the 18 lymphoma patients' biopsies were stained using standard Immunohistochemistry method. PASD1 antigen was detected by two antibodies which were 2ALCC136 (recognize both PASD1_v1 and PASD1_v2 proteins) & 2ALCC128 (detects only PASD1_v2 protein). **Results:** From the diffuse large B-cell lymphoma (DLBCL) patients, our results show 2 out of 7 samples and 1 out of 7 samples showed positive expression using 2ALCC136 & 2ALCC128 antibodies respectively. Meanwhile, for T-cell lymphoblastic lymphoma patient, only 1 out of 1 sample showed positive expression using 2ALCC136 but no expression detected with 2ALCC128 antibody. Antibody 2ALCC136 stained more samples than antibody 2ALCC128 and the staining was predominantly cytoplasmic rather than nuclear. **Discussion:** This could suggest the important role of PASD1_v1 protein in the lymphomagenesis. We must also highlight the sample limitation in this study and the data should be further validated with a higher number of samples. However, the expression of the PASD1 protein in 42% (3/7 cases) of DLBCL in UKMMC was consistent with the frequency of previously reported data in Caucasian population.

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Antiproliferation effect of *Goniothalamus lanceolatus* root crude extracts on PEO1 and PEO4 ovarian cancer cell lines

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ABSTRACT

Ovarian cancer is the main cause of cancer mortality in gynecological tumors around the worlds. Goniothalamus sp. has been traditionally used for childbirth, fever, food poisoining and snakebites infection treatment. To evaluate the growth inhibition of ovarian cancer cell lines, PEO1 and PEO4 ovarian cancer cell lines were treated with crude extracts from *Goniothalamus lanceolatus*'s root. The *G.lanceolatus* extracts were dissolved in three different solvents which were dichloromethane (DCM) hexane and methanol. Varying concentration (0 to 1000 µg/ml) was used and subjected to MTT assay to determine the cytotoxic effect by measuring the ovarian cancer cell proliferation activities. In vitro antiproliferation effect of crude extracts showed that 50 % of growth inhibition concentration (IC_{50}) on PEO1 and PEO4 ovarian cancer cell lines upon 24 hours of treatment. Lowest IC_{50} values recorded were 28.77 µg/ml in PEO1 and 40.38 µg/ml in PEO4 ovarian cancer cell lines. Interestingly, these lowest IC_{50} values were found when the cells were treated in methanol solvent compared to other solvents. Then, the inhibition activities of PEO1 and PEO4 ovarian cancer cell lines were also found in DCM solvent followed by in hexane solvent. Morphological changes in both PEO1 and PEO4 cells lines were compared to the control using inverted light microscope. Overall, the result indicated that the crude extracts from *G.lanceolatus*'s root caused a dose dependent reduction in the proliferation of ovarian cancer cell lines. Thus, *G.lanceolatus* crude extracts could be used as potential anticancer agents in ovarian cancer cell lines.

Keywords: *Goniothalamus lanceolatus,* ovarian cancer, PEO1, PEO4, Antiproliferation, Anticancer

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Altered proteome profiles and apoptotic induction of acute promyelocytic leukemia cell lines, HL-60 by epigenetic drugs, 5-Azacitidine and Trichostatin A

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ABSTRACT

Background: DNA methylation inhibitor, 5-Azacitidine (5-Aza) and histone deacetylase inhibitor, Trichostatin A (TSA) have the ability to reverse epigenetic modification in leukemia. The apoptotic effects of 5-Aza and TSA play an important role in killing leukemic cancer cells. 2D gel electrophoresis is a technique to study qualitative and quantitative protein changes between different states of a cell. The aim is to investigate proteome profiles in HL-60 cell lines upon treatment with 5-Aza and TSA. **Methods:** The inhibition concentration (IC_{50}) of 5-Aza and TSA on HL-60 cell lines were measured in concentration- and time-dependent manner. Annexin V-stained cells were analyzed by flow cytometry to calculate the apoptosis induction in positive cells. Total proteins of untreated- and treated-HL-60 cells were extracted using rehydration buffer by sonication, quantified the extracted protein samples using RCDC protein assay. 2D gel electrophoresis was used to separate the proteins, which were commassie blue-stained in the gel. **Results:** The IC_{50} values of 5-Aza- and TSA-treated HL-60 were 1.98±0.16 µM and 2.35±0.17 µM for 72 hours. The exposure of 5-Aza and TSA on HL-60 cells were significantly increased (p<0.05) the cells population positive for annexin-V. The apoptotic rates were 48.5%±7.1 and 50.9%±4.6 for 5-Aza and TSA treatment. 2D proteome profiles revealed was as the average number of protein spots in three gels of untreated-HL-60 was 520±18.90, 631±15.56 in 5-Aza-treated and 350±1.53 in TSA-treated. The average matching rate was 82%, 87%, and 86% respectively. Changes in the protein profiles of the untreated-HL60 cells and 5-Aza- and TSA-treated revealed the identification of 4 and 1 protein spots. Whereas, the comparison between 5-Aza and TSA-treated resulted in the identification of 15 protein spots. **Conclusion:** 5-Aza and TSA have anti-leukemic effect on the HL-60 cell lines. 2D proteome profiles of untreated- and treated-HL-60 cells were established and proteins expression were altered after treatment with epigenetic drugs.

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In vitro cytotoxicity effect and *In vivo* Sub chronic Toxicity Profile of Curcumin Analogue DK1

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ABSTRACT

(Z)-3-hydroxy-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (DK1) is novel anti-cancer agent that synthetically derived from curcumin. This substance is widely known for its broad spectrum of biological activities, including anti-cancer, anti-oxidant and anti-inflammatory. To date, the effects of curcumin analog DK1 on the normal function of the host have not been studied. Thus, this study aimed to assess the toxicity profile of curcumin analog DK1 in a murine model. Several assays were conducted such as MTT assay on splenocytes, serum biochemical analysis, immunophenotyping of important immunological markers, macrophage depolarization analysis and antioxidant analysis (FRAP, SOD, MDA, NO). Results indicated that DK1 did not induce any significant cytotoxicity effects on the mice splenocytes *in vitro* and did not cause any abnormal changes or mortality to all mice after the treatment period. Based on the results also there are no significant changes in immunological marker, macrophage depolarization and level of serum biochemical parameters in selected organs. These results also corresponded with the increase in anti-oxidant activity measured using FRAP and SOD and reduction of inflammation activity determined using NO and MDA assay. In conclusion, curcumin analog DK1 could be considered as a safe anti-cancer agent because it did not pose any significant toxicity profile on the murine model.

Keywords: Curcumin Analogue DK1, Sub chronic, Ferric reducing ability of plasma (FRAP), Superoxide radical scavenging activity (SOD), Malondialdehyde (MDA), Nitric Oxide (NO)

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Functional effects of EPHB4 and circEPHB4 in colorectal cancer cell lines

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ABSTRACT

Colorectal cancer (CRC) is one of the most widely diagnosed cancer in men and women worldwide. Circular RNAs are a new class of endogenous non-coding RNAs that are involved in the biological process of various cancers. However, little is known about their roles and mechanisms in cancers, including CRC. Eph/Ephrin receptors play crucial roles in many cellular processes including tumorigenesis and angiogenesis but yet the roles of EphB4 in CRC are unclear and not fully understood. Therefore, we aimed to explore and identify the functional analysis of EPHB4 and its circular RNA form in regulating CRC. For the Gene Ontology (GO) analysis, we identified that circEPHB4-targeted genes were highly involved in histone deacetylase complex for the cellular component, regulation of the nucleobase, nucleoside and nucleic acid regulation for the biological process, and cell adhesion molecule activity for the molecular function analysis. Moreover, via the pathway enrichment analysis using the KEGG database, the target genes were significantly enriched in the FoxO signaling pathway. We analyzed the expression of linear EPHB4 and circEPHB4 in CRC tissues and cell lines, both EphB4 were up-regulated in CRC tumor tissues and CRC cell lines. By targeting the linear EPHB4 and circEPHB4, the migration abilities, the cell cycle and the resistance of colorectal cancer cells towards 5-fluorouracil and Oxaliplatin were reduced. Besides that, silencing the circEPHB4 also affected adhesion to several extracellular matrix proteins such as laminin, fibronectin, collagen I and collagen IV. Collectively, this study has shown that circ-EPHB4 may be a potential regulator in CRC pathogenesis, particularly related to drug resistance and cell adhesion.

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Rhodocytin: A Non Cytotoxic Protein from the venom of Malayan Pit Viper (*Calloselasma rhodostoma*) with potential anti-migratory activity on human colon cancer cells

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ABSTRACT

Colon cancer is one of the most common cancer deaths in the world and second most common cancer in Malaysia. Current chemotherapy and combination with targeted therapy strategies are cytotoxic but are known to have serious side effects. Consequently, research into alternative strategies for colon cancer treatment is necessary. Proteins purified from the venom of *Calloselasma rhodostoma* such as snake venom metalloproteinase, L-amino acid oxidase and snake venom C-type lectin have demonstrated potential anti-cancer activities in various cancer cells, but not in human colon cancer cells. In this present study, rhodocytin; a C-type lectin from the venom of *C. rhodostoma* was investigated. The aim was to determine the cytotoxic and anti-migratory activity of rhodocytin in human primary and metastatic colon cancer cells. Rhodocytin was purified and identified by fast protein liquid chromatography (FPLC) and liquid chromatography mass spectrometry (LCMSMS), respectively. Cytotoxic assessment was performed by colorimeteric MTT assay while anti-migratory was investigated using scratch-wound healing assay. Rhodocytin was successfully purified to homogeneity and was found to be non-cytotoxic in all cell lines including normal cells, even at a concentration of 100 µg/ml. Colon cancer cells treated with rhodocytin exhibited a dose- dependent effect on cell wound closure following 30 hours of treatment. Significant reduction of wound closure rate was noted when the cells were exposed to 100 µg/ml of rhodocytin. In conclusion, the data provides evidence on the potential anti-migratory activity of rhodocytin which suggest potential therapeutic intervention of human colon cancer.

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19-20th September 2018, Auditorium UMBI, Kuala Lumpur**

Comparison of Microcarrier and Microcarrier-free Method for 3D Microgravity Culture of Mesenchymal Progenitor Cells (MPC)

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ABSTRACT

Background. Mesenchymal progenitor cells (MPCs) are multipotent stromal cells which play important roles in tissue repair. MPCs grown under the microgravity condition are known to have greater neuroprotective, anti-inflammatory and regenerative properties than under normal gravity thus have great potential in tissue regenerative therapy. Unfortunately, when MPCs are grown in microgravity simulated by the Rotary Cell Culture System, not all the cells are effectively exposed to microgravity. Cells which remain in continuous free-fall suspension are in microgravity condition while cells which adhere to the vessel walls are not, resulting in undesirable heterogeneous culture within a vessel. To date, there are two common methods of culturing MPCs in a simulated microgravity condition, the microcarrier and microcarrier-free method. However, no study had compared the effectiveness of the two methods in creating homogenous microgravity environment for MPCs. This study aimed to compare the effectiveness of microcarrier and microcarrier-free method in achieving a MPC culture system in which cells are evenly exposed to microgravity. **Methods**. Human embryonic stem cells (hESC) were first directed to differentiate into MPCs. MPCs were characterized by immunocytochemistry staining and flow cytometry analysis of typical MPC markers. MPCs were then grown with or without microcarriers under the 3D simulated microgravity condition. The morphology, growth rate, number of MPC clusters adhered to the vessel were assessed for each condition. **Results.** MPCs differentiated from hESC were found to express MPC positive markers, CD73, CD44, CD90, CD13, CD105, CD166, CD147 and Nestin and were negative for MPC negative markers HLA-DR, CD45, CD138 and CD34. The MPCs grown on microcarriers were found to exhibit greater growth rate and did not adhere to the vessel wall as much compared to MPC grown without microcarriers. **Conclusion**. Microcarrier-based method is more effective than the microcarrier-free method in producing MPC culture which is evenly exposed to the simulated microgravity condition.

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Effect of Partially Hydrolyzed Guar Gum (PHGG)-Based Prebiotic Supplement on *Bifidobacterium Sp.* Population in Gut Microbiota from Cancer Patients Underwent Pelvic Radiotherapy Treatment

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ABSTRACT

Radiotherapy is an effective treatment to manage pelvic cancer patients. However, imbalance of gut microbial community due to the radioactive exposure causes side effects particularly, diarrhea among the patients. In effort to reduce such discomfort, prebiotics supplement offers significant relieve by supporting good bacterial growth to maintain healthy gut environment. In this study, partially hydrolyzed guar gum (PHGG) was supplemented as prebiotic to pelvic cancer patients throughout radiotherapy procedure. Aim of the study to evaluate the efficacy of PHGG on promoting growth of colon's good bacteria, *Bifidobacterium sp.* between intervention and controlled groups (PHGG-based prebiotic intervention, n=14 and maltodextrin as placebo intervention, n=16). Stool samples were collected at five time-points, starting at day 0 as baseline, before and during radiotherapy treatment (day 7, 14 and 28), until the end of intervention (day 40-42) and were extracted for DNA samples as template for qPCR analysis to investigate population of all bacteria species and *Bifidobacterium sp.* The population of *Bifidobacterium sp.* in patients treated with PHGG-based prebiotic was higher compared to controlled group throughout the experiment. Based on individual dataset, 9 out of 14 patients showed increase of population after taking PHGG before radiotherapy at the range of 1.4 to 38.1 fold. At day 14 after start or pelvic radiotherapy, 9 out of 12 patients showed increase of population. However, only two patients possed consistent increment of the bifidobacteria's population during the PHGG-based prebiotic intervention and the effect was treatment-dependent that the bacteria number dropped after completion of intervention. There are many factors that could contribute to the outcome, particularly by daily diet, stress level and other physiological condition of patients. By use of microbiome profiles for risk assessment and manipulation of the intestinal flora, prevention and treatment of radiation enteropathy could be possible for long-term cancer survivors.

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Mutant p53 interferes with p63 regulation of miR-205 in triple negative breast cancers

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ABSTRACT

Driver mechanism in triple negative breast cancers (TNBCs) relapse is poorly understood. TP53 has been shown to be one of the most significant regulators in preventing the development of TNBCs. Mutations of the p53 gene can lead to overexpression of aberrant misfolded p53 proteins which led to p63 formation complexes. These complexes consequentially abrogate transactivation of p63 target gene, miR-205. However, p63 function may be compromised by mutant p53. Therefore this study aims to elucidate miR-205 regulatory mechanism by p63 through p53-mutants and to define differential miR-205 regulation by p53-mutant classes (structural and contact mutants) across TNBC cell lines. Differential gene expression analysis of GEOdata (GSE58812) was carried out to identify pathways involved in the metastatic / diseased patients. Data was generated using the Transcriptome Analysis Console (TAC) software. TP53 siRNA was transiently transfected in a panel of TNBC cell lines (good outcome and good outcome). Expression level of miR-205 was assessed by RqPCR, and the data was normalized against RNU6. Significant genes derived from the differential analysis showed that these genes were involved in the p53 signaling pathways. Inconsistent variations of miR-205 transcriptional activation were observed. Significant reductions of miR-205 were seen in both good outcome (HCC1395 and HCC70) and poor outcome (HS578T) cell lines. Recovery of miR-205 were detected in MDA-MB-231, SUM159 (poor outcome) and HCC1937 (good outcome). These data suggested that p53 is a key player in TNBCs imposing DNA damage involvement led to uncontrolled proliferation and genome instability in breast cancers. However, miR-205 may not be specifically regulated by specific p53-mutant classes but it may be differentially regulated by the intrinsic TNBC subtypes (good / poor outcome). Further assessments on p53-mutant types and miR-205 interactions are warranted to provide valuable insights of development in the existing chemotherapy regime for minimizing relapse outcome in TNBC patients.

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Characterization and Distribution of Lactic Acid Bacterial Species from Dadiah, a Traditional West Sumatera Dairy Foods

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ABSTRACT

Indonesia is home to one of the most diverse cuisines and traditional fermented foods. Yogurt-like product dadih is one traditional dairy foods. Dadih is produced and consumed by the ethnic groups of West Sumatra, Indonesia. This study aimed to describe Lactic Acid Bacterial (LAB) characterization and Distribution from Dadiah, A Traditional West Sumatera Dairy Foods. Ten Dadih samples (traditional dairy food) were collected from five traditional manufactures in districs/cities in West Sumatera province, Indonesia, such as Bukittinggi, Padang Panjang, Alahan Panjang, Payakumbuh and Batusangkar. LAB strains were isolated by using MRS agar method and characterized using biochemical identification. Identification of the strains was performed based on 16S rRNA analysis and the phylogenetic tree was drawn to understand the phylogenetic relationship of the collected strains. LAB colonies reached average counts of 5.8 x 10^7 CFU/g Dadih. LAB species were identified based on a conventional phenotypic approach. Twenty nine LAB isolates were randomly selected to analyse its 16S rRNA. Lactobacillus plantarum and Lactobacillus casei were the most frequently identified species according to microbiological and molecular methods. Our results may provide useful information for valuable strain selection as starter cultures for the industrialization of traditional dairy products in West Sumatera, Indonesia.

Keywords: Dadih, Lactobacillus, 16S rRNA, phylogenetic

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Development of a Semiconductor Sequencing-based Panel for Screening Individuals with Lynch Syndrome.

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ABSTRACT

Lynch syndrome (LS) is associated with mutations in mismatch repair (MMR) genes and individuals who harbour one of these mutations have 20 to 65 % lifetime risk of developing colorectal cancer (CRC). The inheritance pattern of these mutations is autosomal dominant; therefore, close biological relatives are also at high risk. Early detection of CRC may lead to better health outcomes and considerable savings in treatment costs. Hence, the aim of this study is to develop a rapid and sensitive method of screening LS. We designed an Ion Ampliseq™ Custom Panel with four MMR genes associated with LS (MLH1, MLH2, MSH6 and PSM2) and two genes which are not categorized as MMR genes (EPCAM and BRAF), for sequencing on the Ion Torrent PGM™ sequencer. Sequencing was performed on 16 DNA samples representing various stages of CRC. The sensitivity for mutation detection was determined by sequencing serially diluted DNA from two human cancer cell lines. Upon completion of NGS, on average, 92 % of reads were mapped to the target region with 98 % uniformity. No amplicons dropout was observed across all samples. Fifty eight variants were identified and chosen to be validated in 19 samples using MassARRAY and Sanger sequencing. A pathogenic variant in MSH2 gene was identified in a 44 years old Dukes' D CRC patient. The Ion Torrent PGM clearly identified a single base pair C to T substitution in MSH2 gene with a variant frequency of 52%. This was also confirmed by MassARRAY. We achieved 92% specificity, 93.4% accuracy and a sensitivity of about 13% allelic frequency for the Lynch syndrome panel. With the development of this rapid and sensitive method, hereditary CRC can be detected at early stage.

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Isotope Tracing Reveals Metabolic Reprogramming in Cells with UHPLC/QTOF and GCMS

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ABSTRACT

Metabolic pathways can be impacted to drive energy and biomass production supporting cancer growth. For a better understanding of altered metabolic pathways in cancer cells, a metabolomics approach in combination with stable isotope labeling technique was developed. The isotopic atom (13C, 15N 18O and 2H, etc) of the tracer molecule can be utilized to reveal the metabolic programming in cancer cells. Mass spectrometry is a powerful tool in measurement of isotopologues of the metabolic labeling with stable isotopes. In this project, GC-MS was used to analyze the intermediate metabolites in glycolysis and TCA cycle. UHPLC/QTOF was utilized to further reveal metabolic reprogramming of glutaminolysis, glutathione biosynthesis and TCA cycle. The oxidative and non-oxidative pentose pathway were studied by using the same chromatography conditions as UHPLC/QTOF. It was found that very little isotopologue M1 of lactate was detected. The non-oxidative PPP is upregulated induced by gene knockout to support cancer initiation and progression. The isotopic fidelity of QTOF allows accurate tracing of stable labels through pathway and MassHunter Vistaflux allows for easy processing of qualitative metabolic flux experiment.

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Combination of Genome Editing Technology and BH3 Mimetics to Determine the Selective Induction of Cell Death in Nasopharyngeal Carcinoma (NPC)

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is an aggressive and is a deadly form of cancer. BCL-2 family proteins are critical regulators of the intrinsic apoptosis pathway. They are up-regulated in many cancers and have become attractive therapeutic targets especially with the development of BH3 mimetics. BH3 mimetics activate apoptosis by binding and inhibiting select anti-apoptotic proteins. The aim of the study is to investigate the functional importance of each anti-apoptotic protein, particularly MCL-1 and BFL-1 for the survival of NPC cells using combination of the CRISPR/Cas9 technology and BH3 mimetics. A human apoptosis RT^2 Profiler PCR Array was first employed to profile the anti-apoptotic gene expressions in both the NPC cell lines. The HK1 cells expressed all the anti-apoptotic genes (*MCL-1, BFL-1, BCL-2, BCL-XL, and BCL-w*). On the other hand, C666-1 expressed all except for *BFL*-1 (undetectable level). Given that there are no specific BFL-1 inhibitors, single guide RNAs (sgRNA) for *BFL-1* were designed to knockout *BFL-1* in the HK-1 cells. The *BFL-1*/sgRNAs were cloned into the PX458 plasmid (pSpCas9(BB)-2A-GFP) and were transfected into the HK-1 cells. To this end we have generated single cell clones of the *BFL-1* knockout HK-1 cells. Parallel to this experiment, we have used selective BCL-2 inhibitors namely ABT-199, WEHI-539, and A-1210477 to chemically dissect the contribution of BCL-2, BCL-xL, and MCL-1, respectively for C666-1 cell survival. The cells were resistant to single agent treatment of these drugs implying that the cells do not solely rely on BCL-2, BCL-XL or MCL-1 for survival. However, combination of all three drugs showed a dose-dependent inhibition of cell proliferation highlighting the collaborative effect BCL-2, BCL-XL, and MCL-1 in maintaining C666-1cell survival.

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A Re-analysis of TCGA Data: Signatures of Gene Expression, DNA Methylation and MicroRNAs of Hepatocellular Carcinoma with Vascular Invasion

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the second major cause of cancer-related deaths worldwide, with a substantial proportion of patients presenting with a late diagnosis. Among factors for its high mortality is the presence of vascular invasion (VI), which is a process of intrahepatic tumour dissemination before the metastatic process. VI is an independent predictor of HCC tumour recurrence and poor prognosis after the surgical liver resection or transplantation. Only macroscopic VI is readily detected by high-resolution imaging techniques before surgery, whereas no available technique can detect microscopic VI. Identification of biomarkers to detect VI before the surgical treatment of HCC patients will help improve the patient's outcome. **Methods:** Here, we re-analysed The Cancer Genome Atlas (TCGA) Liver Hepatocellular Carcinoma (LIHC) datasets and filtered HCC patients into three groups: (i) no VI (NVI=198), (ii) micro VI (MIVI=89) and (iii) macro VI (MAVI=16). Differential gene expression, methylation and microRNA analyses were performed between the groups. Pathway enrichment and gene ontology analyses were performed using the WEB-based Gene SeT AnaLysis Toolkit v. 2017 (WebGestalt) and Database for Annotation, Visualization and Integrated Discovery (DAVID) tool. Analyses with BH-adjusted P-value ≤ 0.05 were considered statistically significant. **Results:** We identified 12 differentially expressed genes (including *FAM155B*, *SLC7A1*, *ODAM* and *GCK*), and 55 differentially methylated genes (DMGs), in a comparison between the MAVI and the NVI groups. Among these genes, *GPD1L* (glycerol-3-phosphate dehydrogenase 1-like) gene appeared in all comparison analyses, in which its gene expression was upregulated, and its methylation expression was reduced in VI groups. **Conclusion:** GPD1L appears to be a good candidate biomarker for VI and has been reported as one of the regulators for HIF-1α-dependent vascular endothelial growth factors and angiogenesis. Thus, *GDP1L* gene expression may offer a potential value as the VI biomarker in HCC progression.

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Anthocyanin and colourant content of *Bouea macrophylla* Griffith and *Bouea oppositifolia* seeds by using chemical extraction

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ABSTRACT

Synthetic food colorants are widely used to improve the attractiveness of numerous foodstuffs. Tartrazine (E102), quinolone yellow (E104), sunset yellow FCF (E110) and Allura Red AC (E129), are the synthetic food colorants being currently indicated as having negative effects such as occurrence of side effects, attention deficit hyperactivity disorder (ADHD), toxicity and allergic reactions. With the increasing demand by consumers for naturally-derived and safer food colourants associated with reduced risk of chronic diseases such as cardiovascular disease and cancer, numerous research have been carried out. Anthocyanins are group of naturally-derived colorants in plants with a renowned impact and demand, mainly due to their prominent colouring attributes bioactive properties and natural preservatives, among other health benefits. *Bouea sp.* popular as kundang fruit, gandaria or plum mango is native to north Sumatra, Peninsular Malaysia and West Java. The *Bouea sp.* fruits had high content of essential amino acids and minerals especially potassium. Limited information was found, as the *Bouea sp.* is underutilized fruit and not popular as other commercially available fruits. Thus, this study were designed to evaluate the anthocyanin and colourant properties of *Bouea macrophylla* Griffith and *Bouea oppositifolia* using chemical extraction. The results showed that the highest yield and total anthocyanin content obtained by using 70% ethanol with hydrochloric acid adjusted to pH 1. Meanwhile the colour analysis indicated the *Bouea macrophylla* Griffith have highest value in lightness and redness compare to *Bouea oppositifolia*. This finding could provide an insight on *Bouea sp.* as a new source of natural food colourants. Hence, more information in cardiometabolic disorder especially to understand the properties of *Bouea sp.* in a view of natural food colourants and biomedical field from scientific merits will be gained, thus enhance their commercial value.

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Research on *In vivo* in Breast Cancer Animal NMU Induced

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ABSTRACT

Background: The administration of N-nitroso-N-methylurea (NMU) is a widely used experimental model in the induction of rodent mammary tumours for investigating breast cancer in women. The carcinogenic-induced tumours arise from terminal end buds, an analogous structure to the terminal ductal lobular unit in humans, which is the proposed site of the origin of ductal carcinoma in situ (DCIS). Substantial evidence suggests that this animal model mimics human breast cancer. **Methods:** Mammary tumour geneses in rats were established by intraperitoneally administering single dose of 70 mg/kg NMU for three consecutive days starting from age of 21 days. Following 30 days' post NMU administration, the rats were palpated twice weekly, and the diameter of mammary tumour was measured and recorded. Rats were sacrificed, and all grossly visible tumour and normal breast pad were excised. The histology of breast cancer tissue was evaluated with Haematoxylin and Eosin staining, while the protein expression of ER, PR (hormone receptors), Flt-1, Flk-1, Flt-4 (angiogenesis receptors) and caspases -3, -6, -7, -8, and caspase-9 (apoptosis receptors) were evaluated by immunohistochemistry (IHC). **Result:** There were no sign of toxicity in rats induced breast cancer. At least one mammary tumour arose of the rats' body. At macroscopic, they were solid and well circumscribed, receiving a good blood supply from collateral vessels. All tumours were 100% malignant histologically with three types of invasive ductal carcinoma (IDC) pattern: cribriform, papillary and Not Other Specified (NOS). Rat mammary carcinomas were aggressive since more than 80% of NMU mammary lesion and were classified as high grade. IHC results showed positive expressions of ER, PR, PPARγ, Flt-1, Flk-1, Flt-4, caspases -3, -6, -7, -8, and caspase-9. **Conclusion:** NMU was recommended in *in vivo* breast cancer animal model and suitable for examining breast cancer development and progression, hormonal status, angiogenesis and apoptosis mechanism of breast cancer.

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Proteomic and immunoreactivity study of *Bungarus fasciatus* (banded krait) venoms from Thailand and Malaysia

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ABSTRACT

Bungarus fasciatus (commonly known as banded krait) is a highly venomous, neurotoxic snake distributed in Southeast Asia. Envenomation by *B. fasciatus* impairs pre-and post- synaptic neurotransmission, leading to systemic paralysis and death without appropriate antivenom treatment. *Bungarus fasciatus* Monovalent Antivenom (BFMAV) produced in Thailand is the only available antidote to treat *B. fasciatus* envenoming. However, its efficacy against the venom of *B. fasciatus* from outside Thailand is uncertain and could be variable due to geographical differences of venom composition and antigenicity. This study was aimed to compare the venom proteomes of *B. fasciatus* from Thailand and Malaysia using reverse-phase high-performance liquid chromatography and sodium dodecyl sulfate-polyacrylamide gel electrophoresis, followed by liquid chromatography tandem mass spectrometry for the proteins identification. Both *B. fasciatu*s venom proteins were dominated by phospholipases A_2 (~60%), followed by Kunitz-type serine protease inhibitors (~21%) and three-finger neurotoxins (~7-10%). The Malaysian *B. fasciatus*, nonetheless, contains a higher abundance of beta-bungarotoxin (5.43%) whereas this protein is not detected in Thai *B. fasciatus* venom. Beta-bungarotoxins (a subtype of phospholipase A_2) block neurotransmission presynaptically; its higher abundance in Malaysian *B. fasciatus* venom correlated with the more potent lethality (median lethal dose=0.91 μg/g) of the venom compared to the Thai species (2.55 μg/g). Despite the differences in the abundance of beta-bungarotoxins and lethality, the venom proteins of *B. fasciatus* from the two region shared common antigenicity as BFMAV exhibited comparable binding activity to both venoms on indirect enzyme-linked immunosorbent assay (ELISA) (half-maximal concentration of antivenom for Malaysia and Thailand, EC_{50} is 11.9±0.63 μg/mL and 10.36±1.11 μg/mL, respectively). Future studies seek to elucidate the neutralization efficacy of BFMAV against neurotoxicity induced by both Malaysian and Thai *B. fasciatus* venoms.

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Profiling of Cellular Circular RNA in Folfox-Resistant Colon Cancer Cells

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ABSTRACT

Chemo-resistance remains as a major obstacle for treatment of colorectal cancer (CRC) patients. However, there is still no clinical biomarker available to predict chemoresistance at early stage of therapy. Circular RNAs (circRNAs) are non-coding RNAs formed by back-splicing events and have covalently closed loops with no poly-adenylated tails. Circular RNAs have been rediscovered in the recent decade with advancements in sequencing technology but little is known about the expression and possible function of circular RNAs particularly in CRC. This research aims to profile circRNAs in Folfox-resistant HCT116 CRC cell line to discover potential biomarkers among CRC patients with chemo-resistance. Normal CRC cell line HCT116 (HCT116-C) was induced with 10 cycles of drug treatment to develop corresponding Folfox-resistant derivative clones (HCT116-R). HCT116-C and HCT116-R cell lines were compared for cell viability in 5-FU and oxaliplatin, wound healing assay, migration and invasion. Cellular RNA was isolated from both cell lines and quantified with Nanodrop and Bioanalyser. Total RNA was converted to cDNA and hybridised for circular RNA microarray. As compared to normal HCT116-C cell line, HCT116-R cell line had higher IC_{50} values with 2.5 to 6-fold change. Migration rate of HCT116-R cell line was 19 percent higher than HCT116-C cell line in wound healing assay. 773 circular RNAs were upregulated and 733 circular RNAs were downregulated in HCT116-R cells as compared to HCT116-C cells. From the results, hsa_circ_0064555 was the most upregulated between HCT116-R and HCT116-C. This circRNA was predicted to bind to hsa-miR-619-3p, hsa-miR-29b-1-5p, hsa-miR-370-3p, hsa-miR-30d-3p and hsa-miR-30a-3p. We have successfully cultured stable HCT116-Folfox resistant CRC cells with distinct characteristics from the parental cell line. We have identified several circular RNAs in the HCT116-R cell line as potential biomarkers to predict Folfox-responsiveness.

Keywords: Colorectal cancer, Folfox, chemo-resistance, biomarkers, molecular targets

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Willingness to Pay for Cancer Genetic Testing in University Kebangsaan Malaysia Medical Centre (UKMMC)

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ABSTRACT

Background: Increasing use of predictive genetic testing to screen for hereditary cancer risk has been commonly assessed by cost sharing practices. Little is known about how demographics, knowledge, attitude and practices may influence individuals' willingness to pay for genetic testing cancer. **Aims:** This article aims to determine factors associated with willingness to pay for cancer genetic testing. **Methods:** A self-administered questionnaire were distributed to 175 respondents in the oncology and day care unit in University Kebangsaan Malaysia Medical Centre (UKMMC) consist of patient and their accompanier (family and community). **Results:** 103 (58%) of participants reported that they were willing to pay for genetic testing for cancer. There were significant associations between status of respondent, gender, race, educational level, income, knowledge and attitude with willingness to pay. **Conclusion:** This is the first study to evaluate the factors associated with willingness to pay not only among the patient but also their family members and community. These findings reveal that some respondents find valuable personal benefit in genetic risk information.

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High expression miRNAs in CML patient responsive to imatinib treatment by Next Generation Sequencing

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ABSTRACT

Background: Imatinib is a first generation tyrosine kinase inhibitor and used as first line treatment for CML. Even though overall survival rate is 85%, relapse occurred around 42% in treatment free patients. Lately microRNAs potential in cancers have been widely studied and Next Generation Sequencing (NGS), known for its high sensitivity, high coverage and high throughput is increasingly used. In combination, these will further characterize CML and beneficial for further improvement in monitoring response to treatment. The objective of this study is to identify miRNAs that have high expression in CML patient responsive to imatinib treatment when compared to normal control by NGS. **Materials and Methods:** A total of 2.5ml peripheral blood was collected into PAXgene® Blood RNA tube from CML patient and normal control. MiRNAs from these participants were purified using PAXgene® Blood miRNA Kit. Next Generation Sequencing was then carried out by preparing libraries using Illumina® TruSeq Small RNA kit and ran on Miseq. Alignment was then carried out using BaseSpace. **Results:** Hsa-miR-15b-5p was found expressed 22 times higher in CML patient responsive to imatinib when compared to normal control, while hsa-miR-30b-5p and hsa-miR-150-5p were expressed 1.3 times higher than the normal control. The rest of high expressions miRNAs have expression around 1.3 times. Higher expression could indicate increased BCR-ABL1 transcripts in patients. **Conclusion:** Therefore these miRNAs have potential as biomarkers in monitoring response to imatinib treatment. Further analysis in substantial clinical samples is required to determine their significant involvement in treatment response.

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The Effects of Curcumin Analog, DK8 on the Apoptotic and Metastatic Process of Colon Cancer Cells, HT29 and SW620 *in Vitro*

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ABSTRACT

Colorectal cancer (CRC) is the third most common type of cancer worldwide and a leading cause of cancer death. There are many treatments that can be applied such as surgery, radiation, and chemotherapy. However, these treatments may give side effects to the patients such as loss of appetite, alopecia (hair loss), constipation and vomiting. One of the alternative ways to fight cancer is by using natural products. Curcumin is a compound of the rhizomes of *Curcuma longa* that possess a broad range of pharmacological activities. Curcumin has been studied for decades but due to its low bioavailability, its usage as therapeutic agent has been compromised. This leads to development of chemically synthesized curcuminoid analogue, DK8. This study aims to examine the cytotoxicity, apoptosis and anti-metastasis potential of DK8 against colon cancer cell lines, HT29 and SW620. The cytotoxic assay (MTT) has been conducted in both cell lines; HT29 and SW620 and the inhibitory concentration (IC_{50}) for DK8 in SW620 and HT29 were 7.5±1.19 µg/mL and 9.8±0.55 µg/mL respectively. Next, to examine the morphological changes between cells after the treatment, AO/PI assay was conducted followed by flow cytometry analysis; Annexin V/FITC and cell cycle analysis. Both cells underwent apoptosis since relative increase of the sub G0/G1 population was observed. Furthermore, a prominent anti metastatic ability of DK8 compound was demonstrated by migration and invasion assay. A significant reduction of migrated and invaded cells was observed. As a conclusion, DK8 could be considered as one of potential candidates as an anticancer agent for colon cancer.

Keywords: Colorectal cancer, DK8, cytotoxicity, apoptosis, metastasis

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Characterization of molecular features in colorectal cancer tissue by MALDI imaging

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ABSTRACT

Cancer tissues comprise of heterogenous populations of cells that exhibit diverse behaviour and morphological changes. Current clinical diagnosis and tumor classification that rely on conventional histology examination have several limitations and can be challenging as some regions are indistinguishable histologically. To date, there is still a lack of molecular markers indicative of changes that occur during cancer development for early detection, accurate disease diagnosis and classification. Molecular profiling is of great value to characterize cancer based on their distinct molecular phenotypes. Matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry is a technique that allow direct profiling of the expression and distribution of endogenous molecules on intact tissue section, hence preserving the morphological details. One of the key advantages of MALDI-MSI is that it enables the correlation between the molecular data with the underlying histopathological changes to facilitate accurate disease classification. In this study, we aim to identify molecular signatures that could discriminate between cancerous and normal cells in colorectal cancer tissues by using MALDI imaging. Colorectal cancer tissue was sectioned, transferred onto Indium-Tin-Oxide (ITO)-coated slides and sprayed with sinapinic acid matrix. The tissue section was subjected to MALDI imaging analysis and subsequently stained with hematoxylin and eosin (H&E). Mass spectra data was classified by hierarchical clustering by similarity and compared with the histology. We identified unique signatures of mass ion peaks that are associated with the tumour region of colorectal cancer. Our preliminary results demonstrate the usefulness of MALDI imaging for detecting clinically relevant molecular alterations in which the specific molecular pattern could potentially serve as biomarkers to distinguish between colorectal cancer and normal tissue. However, further investigation is needed to confirm these findings.

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Pickled Food and Stomach Cancer: A Systematic Review of Observational Studies in Asia

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ABSTRACT

Background: Stomach cancer is one of the top-five most prevalent cancers in the world. It is also a leading cause of mortality and ranks among the top-three cancers with the greatest number of annual mortalities. Although the incidence is gradually declining, Asia remains the region with the highest incidence worldwide and literatures point towards pickled food consumption as one of the major associating factors. We conducted a systematic review to peruse the evidence of latest studies done in Asia. **Methods:** Original articles were systematically searched using the PICO strategy by applying keywords, namely “stomach cancer”, “pickled food”, and their MeSH terms. Titles and abstracts from databases including PubMed, Scopus, and Google Scholar were explored. Only studies published in English and conducted in Asia within the last 10 years were included. Our search returned 141 articles which were each scrutinized by two reviewers to determine suitability with the research question. Nine articles met the criteria set for systematic review; and from these articles, eight were subjected to meta-analysis. **Results:** All accepted articles were case-control studies, which consisted of six hospital-based and three population-based studies. Most studies were conducted in China (five), followed by Turkey (two) and one each in India and Iran. All studies reported significant increased risk of stomach cancer with pickled food consumption. Test for heterogeneity revealed the eight studies to be significantly heterogeneous (chi-squared: $p < 0.001$, I^2 statistic: 87%). The measure of pickled food consumption quantification varied between studies, and may have caused statistical heterogeneity between the results. Computed using random effects model, pooled OR showed positive association between consumption of pickled food and stomach cancer (OR = 3.42; 95% CI: 2.28 – 5.12). **Conclusion:** The findings of this review may offer insight on stomach cancer prevention and into steering the national dietary policy on pickled food consumption.

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PASD1 expression in Colorectal Carcinima and Polyps Patients at UKM Medical Centre (UKMMC)

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ABSTRACT

Background: Per ARNT Sim Domain containing Repressor 1 (PASD1) is one of the cancer testis antigens (CTAs) which have restricted expression in normal tissues but widespread expression in cancers. This makes PASD1 as an attractive immunotherapy target. Two *PASD1* transcripts have been identified namely *v1*, which encodes 639 aa N-terminus while *v2*, encodes a longer protein (773 aa) with a unique C-terminus. This study aims to investigate the expression of PASD1 in the colorectal patients from UKM Medical Centre. **Method:** Formalin-fixed paraffin-embedded (FFPE) sections from the 8 colorectal carcinoma (CRC) and polyps patients' biopsies were stained using standard Immunohistochemistry method. PASD1 antigen was detected by two antibodies which were 2ALCC136 (recognize both PASD1_v1 and PASD1_v2 proteins) & 2ALCC128 (detects only PASD1_v2 protein). **Results:** Our results show 3 out of 5 CRC samples and 2 out of 3 polyps samples showed moderate positive expression of PASD1 using both 2ALCC136 & 2ALCC128 antibodies. The positive staining was both in the cytoplasmic and nuclear region. There was no clear association between the location of PASD1 staining and the sample type and stages. **Discussion:** This could suggest the important role of PASD1 protein in the colon carcinogenesis and polyps. We must also highlight the sample number limitation in this study as this is a preliminary data. This is the first study reported on the expression of PASD1 in patients' colon tissue.

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Bioinformatics and Structural Analyses of Mutation in Malaysian Patients with Argininosuccinate Lyase Deficiency

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ABSTRACT

Argininosuccinatelyase deficiency (ASLD; MIM #207900) is caused by the mutations in the human *ASL* gene (MIM #608310), in which affects the urea cycle enzyme argininosuccinatelyase (ASL). Mutations of the enzyme cause various clinical effects which result in neurological defects or death. To date, close to 140 pathogenic mutations are reported, and majority of those are missense mutations. In this study, we sought to identify mutations in suspected ASLD patients. We further investigated the effect of mutations by using bioinformatics and structural analyses. A total of 22 patients were included in this study. Polymerase chain reaction and sequencing analysis were employed to identify the mutations, while 7 in silico servers, (FATTHM-XF, Mutation Taster 2, M-Cap, MutPred2, I-Mutant3, CUPSAT and Site Director Mutator (SDM)) and structural examination (Pymol) were used to further inspect the effect of those mutations. Molecular analysis identified eight different missense mutations in 10 patients. Of these, four were novel mutations, R146G, L199V, L260F and S447T, and the other four mutations, R146W, R186W, R193Q and R213Q were already reported in the literature. The novel mutations were confirmed by their absence in 100 chromosomes from the normal population. In silico servers predicted all novel mutations led to the development of ASLD. Further structural examination showed the novel mutations, R146G, L199V, L259F, were located in domain 2, while S447T was located in domain 3. These mutations were observed to disrupt the hydrogen bond networks among their neighboring residues. Interference to these two domains probably disturbed the catalysis activity in ASL enzyme that cause excessive accumulation of argininosuccinic acid (ASA) in tissue and body fluid. In conclusion, this is the first report of mutations in ASLD Malaysian patients. Bioinformatics and structural analyses predicted that all novel missense mutations are highly likely to cause the occurrences of ASLD.

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Quantitative mass spectrometry analysis of AGR2-reconstituted cancer cell identifies multiple AGR2 interacting proteins

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ABSTRACT

AGR2 is a cancer-associated endoplasmic reticulum (ER) protein that belongs to the protein disulfide isomerase (PDI). AGR2 is overexpressed in various types of cancer, yet the molecular mechanisms underlying its properties and functions are poorly understood. Identifying the AGR2 protein-protein interaction network can further delineate the role of AGR2 and associate it with known pathways, particularly in tumorigenesis. Here, we constructed a low expressing AGR2 vector which is under the control of weak Rous sarcoma virus (RSV) promoter. We delivered the wild type (wt)-AGR2 and AGR2 harboring canonical ER-retention motif KDEL (AGR2-KDEL) via transient transfection into AGR2-non expressing FLO-1. This allows an analysis of how AGR2 protein expression reprograms intracellular signaling and to unravel affected dominant proteins and pathways. We performed quantitative mass spectrometry using tandem mass tags (TMT) isobaric labeling which can present the global view of cellular proteome dynamics of these AGR2-reprogrammed cells. We identified 1224 proteins for relative quantitation across the experimental conditions. TMT relative quantitation showed that the cellular proteome of reconstituted wt-AGR2 and AGR2-KDEL cells showed marginal effects compared to the RSV empty vector cells. However, the AGR2-KDEL cells showed that most proteome were upregulated compared to wt-AGR2 cells, suggesting that these two AGR2 variants with different localizations have specific distinct signaling pathways. Functional enrichment demonstrated that the top upregulated proteins consist of exosomal and lysosomal proteins suggesting potential roles of AGR2 in their signaling pathways. These system-wide screens identify multiple dominant proteins of AGR2-signaling axis and further defined AGR2 interactome. This study will also provide new insights into disease mechanism and identifies the ‘druggable’ stage in oncogenic pathways.

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Mitochondrial DNA Mutations in Malaysian Female Breast Cancer Patients

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ABSTRACT

Background: The development of breast cancer in Malaysia has been associated with genetic predisposition and lifestyle factors but recent studies have shown that mitochondrial metabolism may also play an important role. In the present study, we aimed to explore the variation in the mtDNA mutations associated to mitochondrial activity in female breast cancer patients. **Methods:** Female breast cancer patients (n=20) without neoadjuvant treatment were recruited. Twenty matched breast tumours with corresponding normal breast tissue were obtained at the time of mastectomy surgery and snap frozen in liquid nitrogen. Total DNA was extracted from all the samples and entire mtDNA (16.6kb) was amplified using long range PCR amplification. The amplified PCR products were sequenced using high-coverage next generation sequencing platform. MtDNA variants were called and annotated using bioinformatic tools. **Results:** A total of 19 out of 20 tumours exhibited at least one somatic mtDNA mutation. Among the 81 somatic mutations identified, 46 novel mutations were found. The majority 46 (57%) of the somatic mutations were in the coding region whereas only 16% of the mutations occurred in the D-loop. Notably, 33 out of 46 somatic mutations in the protein-coding regions were non-synonymous mutations and such amino acid substitution may exert a deleterious effect on mitochondrial metabolism. Additionally, 250 polymorphisms were identified and 24 of them were novel polymorphisms. **Conclusion:** In conclusion, mtDNA mutations in breast cancer has been found to occur both within and outside of the D-loop region. Somatic alteration in the coding regions may act as a precursor in the mtDNA mutagenesis in breast cancer. The catalogue of mutations presented in this study is the first evidence of alterations in the mtDNA in breast cancer of Malaysian female patients and the findings may serve as a reference for future studies that involve breast cancer mitochondrial genomes in Malaysia.

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The effects of LDLR mutation in hypercholesterolemia using in-vitro cell line model

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ABSTRACT

Familial hypercholesterolemia (FH) is an autosomal dominant metabolic disorder characterised by elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in the blood plasma. Increased LDL-C in the artery can cause development of atherosclerosis which will lead to cardiovascular disease (CVD). The prevalence for homozygous FH (HoFH) is very low (1 in a million) but heterozygous FH (HeFH) which is the most common form of the disorder is affecting 1 in 250 individuals worldwide. The primary cause of FH is due to mutation in the low-density lipoprotein receptor (*LDLR*) gene which results in complete or partial defect of circulating LDL-C uptake. Current data from The Malaysian Cohort Study (TMC) showed that approximately 44.2% of Malay participants suffered from hypercholesterolemia and several novel mutations in *LDLR* gene had been identified using whole exome sequencing technique. We chose the most frequent mutation observed among this cohort (c.T2037A) for functional analysis in order to understand the pathogenicity and the mechanism involved in the development of FH. Mutant *LDLR* gene was stably transfected into HEPG2 cell line in order to characterise its function in regulation of cholesterol mechanism including LDL internalisation, uptake and clearance. Expression of the mutant gene will be measured at post-transcriptional and post-translational levels along with other sequester proteins such as PCSK9 and APOE. This functional study will elucidate us on the mutational spectrum of FH among Malay cohort.

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Regulation of L-type amino-acid transporter 1 (LAT1) by constituents of *Centella asiatica* in human T-cell acute lymphoblastic leukemia

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ABSTRACT

L amino-acid transporter 1 (LAT1) supports the growth and survival of T-cell lymphoblastic leukaemia and is a potential therapeutic target for cancer. *Centella asiatica* (CA) or mainly known as 'pegaga' among local Malaysians possesses many pharmacological effects due to their unique constituents that are not found in other plants. However, the effect of the constituents on *LAT1* regulation in acute lymphoblastic leukemia (ALL) cells has not been explored. Hence, in this study, we investigated the direct cytotoxicity of four main constituents of CA in regulating of *LAT1* expression and possibilities of their inhibitory function in leukaemic cell proliferation. The cytotoxicity of CA constituents on CCRF-CEM cell were determined by MTT assay at eight different concentrations by two-fold serial dilution (highest concentration used was 200mM). The concentration required for a 50% inhibition of viability (IC_{50}) was determined graphically using GraphPad software and the effect of the samples on the proliferation of CCRF-CEM was expressed as percent of cell viability. The IC_{50} value of the constituents obtained was used for further cell treatment followed by total RNA isolation of untreated and treated cell. One-step real-time quantitative RT-PCR assay was performed to quantify the *LAT1* mRNA expression level followed by assessment of *Akt* expression, a downstream effector of PI3K activation. From the graphs, the IC_{50} value of asiaticoside, madecassoside, asiatic acid and madecassic acid were recorded to be 10mM, 40mM, 20mM and 80mM respectively. Quantitative RT-PCR result showed that the expression level of *LAT1* was mostly downregulated ($p<0.05$) after cell treatment with these compounds as compared to untreated cell. *AKT1* was found to be overexpressed by the constituents, which suggest possible activation of PI3K that may result in signals for cell survival, cytokine gene induction, and cell cycle progression in T cells. In conclusion, our results show that inhibition by CA constituents on *LAT1* expression in T-ALL cells could be used as an interesting therapeutic strategy to treat hematopoietic malignancies.

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DNAH11 and HYDIN gene mutations revealed autosomal recessive inheritance in Primary Ciliary Dyskinesia (PCD)

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ABSTRACT

Background: Primary Ciliary Dyskinesia (PCD) is a rare, ciliopathic, autosomal recessive disease associated with ciliary dysfunction. The disease is very heterogeneous in nature and the clinical phenotype can be varies significantly. Thus, the clinical diagnosis of PCD is very challenging, therefore molecular analysis is important in order to confirm the clinical diagnosis. To date, more than 32 PCD genes have been described. In this study, we performed whole exome sequencing (WES) to identify the causative mutations in a patient with Primary Immunodeficiency Disease (PID). **Methods:** Trio-analysis (WES) was performed using Ion AmpliSeqTM Exome RDY Kit in a 10-year-old boy and his parents. The exome data was analysed using Torrent Suite version 5.0.4 and annotated using ANNOVAR. Polymorphisms with an allele frequency > 0.01 were excluded (1000 Genomes Project, 6500 NHLBI exomes, Maximum Population Frequency) and the remaining variants were subsequently filtered based on de-novo mutations, autosomal recessive and X-linked recessive. **Results:** We did not detect any homozygous and X-linked mutations associated with PCD in this patient. However, we identified biallelic mutations in DNAH11 and HYDIN genes. From the mother, two heterozygous mutations were identified, DNAH11 (ENST00000409508:p.S2445L) and HYDIN (ENST00000393567:p.D3862N). From the father, two heterozygous mutations were identified, DNAH11 (ENST00000328843:p.L1432W) and HYDIN (ENST00000393567:p.A3796V). These candidate mutations were confirmed by Sanger sequencing. In silico analysis revealed that all mutations were predicted to be deleterious. **Conclusions:** Biallelic mutations from the DHAH11 and HYDIN genes may be responsible for PCD phenotypes observed in the patient. Both genes are reported before to be associated with PCD, in which both are known to be directly involved in the cilia structure development and motility. WES is important in the clinical setting to assist the clinicians for accurate diagnosis of rare and heterogeneous diseases such as PCD.

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Attitude and practice on the use of adjuvant endocrine therapy among breast cancer patients – A qualitative study

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ABSTRACT

Adjuvant endocrine therapy (AET) such as tamoxifen or aromatase inhibitor is used to lower the recurrences of breast cancer and increase patients` survival rate. However, there is lack of studies exploring the attitude and practice of breast cancer patients receiving adjuvant endocrine therapy (AET) particularly in Malaysia. This study was conducted to explore on the attitude and practice on the use of AET among breast cancer patients in Malaysia. This study was conducted at Oncology clinics UKM Medical Centre by interviewing 30 post-menopausal breast cancer patients on at least 3 months of AET. Patients underwent in-depth interviews exploring their attitude and practice while on AET using a semi-structured protocol. The interviews were transcribed into verbatim which was analysed using the NVivo software by thematic analysis. There were five main themes for attitude towards AET: (1) barriers in taking AET, (2) risks of using AET, (3) benefits using AET, (4) spiritual beliefs, and (5) beliefs on complementary and alternative medicine (CAM). For practice, six themes were obtained: (1) correct use of AET, (2) appointment adherence, (3) information-seeking behaviour, (4) counselling services obtained, (5) side effects of AET experienced and (6) usage of CAM. In conclusion, there are several themes concerning attitude and practice of breast cancer patients receiving AET were identified through this study. Findings from this study will be utilized in the development of a survey instrument to determine attitude and practices on the use of AET among breast cancer patients.

Keywords: Adjuvant Endocrine Therapy, Breast Cancer, Qualitative Study, Attitude, Practice