26th August 2014 (Tuesday)
1000-1045
Sabah Room

PLENARY LECTURE 1

Chairperson: Leslie Lai

PL1. Use of endogenous biomarkers to achieve personalized immunosuppression

Michael Oellerich

Institute for Clinical Chemistry, University Medical Center Göttingen, Germany

Introduction: Transplantation biomarkers attract much attention because there are still unresolved problems. Irreversible chronic rejection and side effects of standard immunosuppression limit long-term outcome. There are limitations to how immunosuppressive drugs are currently monitored. Therapeutic drug monitoring is more useful to prevent toxicity than to predict efficacy. Biomarkers are needed that can accurately diagnose or predict complications at their earlier stages. *Materials & methods*: Various strategies are currently being evaluated, including biomarkers of immune response (IL-2 expression in CD8+ T cells, DSA), predictors of tolerance (e.g. nTregs, B-cell differentiation genes), and markers of graft injury. A particularly promising new approach for early detection of graft injury is based on the determination of graft-derived circulating cell-free DNA (GcfDNA) using droplet digital PCR. This assay takes advantage of a SNP panel that can be used for any donor/recipient combination for exact quantification of GcfDNA percentage. GcfDNA has the advantage that it directly interrogates the health of the donor organ ("liquid biopsy"). *Results*: In a recent study, subtherapeutic tacrolimus levels < 8 µg/L, HCV+ and rejection episodes, but not cholestasis, were associated with significantly elevated GcfDNA. The significant increase of GcfDNA was already observed 4 to 6 days before full-blown acute rejection. *Discussion*: Optimal biomarker/TDM combinations which are practical and cost-effective (e.g. GcfDNA, nTreg (TSDR), regulatory gene sets, DSA) are needed. Molecular markers are available to assess the likelihood of acute rejection or late graft loss due to antibody-mediated rejection. GcfDNA could be helpful to identify recipients with ongoing undetected graft injury leading to chronic rejection, at risk of acute rejection, and who would benefit from immunosuppression minimization or more potent immunosuppression. In the future, personalized immunosuppression will shift emphasis from reaction to prevention which could make immunosuppressive drugs safer, more effective, and reduce the cost of health care.

26th August 2014 (Tuesday)
1045-1130
Sabah Room

PLENARY LECTURE 2

Chairperson: Veera Sekaran Nadarajan

PL2. Clinical application of next generation sequencing in managing cancer

David S. Wilkinson

Virginia Commonwealth University, Richmond, VA, USA

The completion of the Human Genome Project and the subsequent development of massively parallel sequencing platforms that can provide reliable sequence information within a clinically useful time frame and at a reasonable cost have moved the dream of personalized (or precision) medicine from the research lab to the clinic. Inspired by the success of several well-known targeted cancer therapies, such as imatinib, which targets the *BCR/ABL1* fusion protein in chronic myelogenous leukemia, oncologists have long sought to use comprehensive genomic information to develop individualized treatment regimens that will maximize benefits and minimize toxicity. Commercially available next generation sequencing (NGS) instruments range in price from around $40,000 to $600,000, with reagent/chip cost/run ranging from $350 to $5000. There are also significant costs for data analysis. Widespread deployment of NGS will probably progress from targeted panels of genes with mutations known to be informative in cancer, to whole exome and eventually whole genome sequencing. However, transitioning from the research mode to the clinical mode may prove more difficult than originally thought. None of the platforms have yet been approved for clinical use in cancer management by the United States Food and Drug Administration, but such approval is expected in the near future. At the Virginia Commonwealth University Health System Molecular Diagnostics Laboratory, we have implemented the Life Technologies IonAmpliSeq™ Cancer Hotspot Panel v2, which can survey hotspot regions of 50 genes, including both oncogenes and tumor suppressor genes. In the early phase of deploying this platform, we have focused on a limited number of mutations with proven clinical utility, simply replacing older technology with NGS. As we gain experience, the gene and mutation panel reported will expand.

27th August 2014 (Wednesday)
1030-1115
Sabah Room

PLENARY LECTURE 3

Chairperson: Zahari Noor

PL3. O dear! My patient just died on me – A forensic perspective on iatrogenic lethality

Gilbert Lau

Forensic Medicine Division, Health Sciences Authority, Singapore

In many jurisdictions, iatrogenic deaths are subjected to some form of statutory medico-legal investigation or inquiry, requiring the expertise of forensic pathologists who, together with other medical professionals, may also be called upon to testify in the ensuing judicial proceedings.

A comprehensive forensic evaluation of an iatrogenic death may extend beyond the conduct of a complete autopsy, supplemented by various ancillary investigations, to include a protracted process of clinico-pathological correlation. In principle, not all fatal adverse medical events are necessarily iatrogenic in nature. Even when an iatrogenic injury is demonstrable at autopsy, the attending pathologist should weigh the implications of such a finding against the underlying natural disease processes that prevailed at the time to death, so as to determine its actual significance in relation to the causation of death, which may be due to a combination of iatrogenic and natural causes.

The pathological and medico-legal complexities associated with such deaths have been further complicated by the therapeutic imperative afforded by advanced medical technology and clinical expertise, resulting in the aggressive treatment of gravely ill patients who often suffer from extensive and serious co-morbidity. As these 'heroic' interventions are obviously associated with heightened risks of iatrogenic injury and lethality, they beg the question of whether the pursuit of such a management policy is truly in the best interests of the patients concerned. While it is not given to a forensic pathologist to opine on matters pertaining to standards of care, it is entirely proper for him to draw attention to any cause for concern revealed by the post-mortem examination.

As the information obtained from these, admittedly tedious and onerous, autopsies serves to inform medical audit and enhance patient safety, the entire process may be regarded as an extension of the traditional roles of forensic pathology in serving the administration of justice and promoting public safety in general.

27th August 2014 (Wednesday)
1400-1445
Sabah Room

PLENARY LECTURE 4

Chairperson: Yasmin Malik

PL4. Beta-lactam, carbapenem and quinolone antimicrobial agents: growing evidence of the importance of therapeutic drug monitoring.

Deborah Marriott

St. Vincent's Hospital, Sydney, Australia

Antibiotics have revolutionized medical care since their inception over 60 years ago. However despite the availability of antibiotics that are active against the majority of pathogens treatment failure still occurs. Dosing of antimicrobial agents is often established in healthy volunteers or the 'standard' patient where predictable pharmacokinetics are assumed to result in the antimicrobial dose recommended in the product information to reliably achieve a target concentration range. However many patients are 'difficult' patients with factors such as augmented renal clearance, altered volume of distribution, obesity, and the presence of interacting drugs making the achievement of the target drug exposure much more problematic. The assumption of 'one size fits all' is increasingly recognized to be flawed, particularly in critically ill patients where the physiology is significantly altered by the presence of sepsis. Recent data confirms that beta-lactam, carbapenem and quinolone antibiotics are frequently under-dosed, particularly in septic patients, although there is mounting evidence that standard dosing may be inappropriate in general ward patients, outside the setting of the intensive care unit. Given that failure to achieve target concentrations is common in some patient populations, reduced pathogen susceptibility is increasingly reported and there is a clear relationship between exposure and effect for many antimicrobial agents therapeutic drug monitoring is likely to result in a significant improvement in patient management.

28th August 2014 (Thursday)
0830-0915
Sabah Room

PLENARY LECTURE 5

Chairperson: Lai-Meng Looi

PL5. International standards and laboratory quality

Stewart Bryant

Brisbane, Australia

The paper will discuss the range of adverse events that may happen to patients if there is not an effective quality system in the medical laboratory. The events discussed will be drawn from personal experience, the medical literature, and the lay press.

The provisions of the ISO Standard 15189 (*Medical Laboratories -- Requirements for quality and competence*) will be used as the basis for categorising these errors.

These provisions are Personnel qualifications, Training, Competence assessment and Performance monitoring, Continuing education and professional development, Accommodation and environmental conditions, Laboratory equipment, reagents, and consumables, Pre-examination processes. Examination (analytical) processes, Ensuring quality of examination results, Post examination processes, Reporting of results and, Information systems.

The functions and activities of the International Standards Technical Committee (ISO/TC 212) which is responsibile for Medical Laboratory will be discussed.

The use of International Standards by various regulatory and accreditation authorities will be highlighted.

The way in which we as individual professionals and professional organisations can be involved in the development and review of international standards will be discussed.

The main avenue for engagement is through the National Standards Organisations (NSO) which may have a 'mirror committee' to TC212. For professional organisations that do not have access through a NSO, the WASPaLM Liaison to ISO/TC212 can be a useful conduit.

28th August 2014 (Thursday)
1400-1445
Sabah Room

PLENARY LECTURE 6

Chairperson: Arni Talib

PL6. Immunohistochemistry in the era of personalised medicine

Manuel Salto-Tellez

School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland, UK

Immunohistochemistry (IHC) plays a central role in the histopathological classification of diseases, including cancer. More recently, the importance of immunohistochemical staining is increasing: while IHC usage in diagnostics is invaluable, the genetic and therapeutic significance of biomarker immunostaining has become equally relevant.

The first part of this lecture (as presented in *Salto-Tellez et al J Clin Pathol. 2013 Jan;66(1):58-61*) will review the three distinct roles of IHC and address their individual impacts on modern diagnostic pathology: (1) diagnostic IHC; (2) genetic IHC and (3) therapeutic IHC. By doing so, we will characterise the different analytical processes that are required in the three approaches to IHC usage stated above, as well as the clinical significance and overall importance in patient management. This will allow us to hypothesize on the most appropriate laboratory environment and detection methods for the future.

The second part of this lecture will address how three main new developments in molecular diagnostics (namely: (a) the use of high-throughput technologies, b) the value of biomarker analysis at different level of the basic dogma of molecular biology and c) the opportunity to test other biological samples such as peripheral blood) will affect IHC as a key player in personalized medicine.

26th August 2014 (Tuesday)
1330-1500
Selangor Room

Symposium 1: Forensic cardiopathology

Chairpersons: Mohammad Shafie Othman; Razuin Rahimi

S1a. Sudden cardiac deaths in young adults

Jagdish Butany

University of Toronto, Canada

Sudden Cardiac Death (SCD), is unexpected natural death due to cardiac causes, most commonly ventricular arrhythmias. The underlying cause varies with age, with older individuals commonly having underlying coronary disease, younger individuals may have a range of underlying diseases, from congenital heart disease to myocardial structural disease and the dreaded Sudden Unexplained Cardiac Death Syndrome(SUDS). In young people the common underlying causes are congenital heart disease, cardiomyopathies and the "channelopathies". Most cases will have underlying disease that had not been diagnosed or was "silent", however a small number will need a "molecular autopsy", for diagnosis of underlying genetic abnormalities. A major reason for studying these cases is the implications of the disease and the findings for surviving members of the family. This presentation will concentrate on SCD in the young adult.

At the end of this session you should have some idea about the approach to examination of the heart, the common causes of SCD and their pathology.

S1b. A review of sudden cardiac deaths in children

Marta Cohen

Histopathology Department. Sheffield Children's Hospital, Sheffield, UK.

Sudden cardiac death (SCD) is defined as death that is abrupt, unexpected, and due to a cardiovascular cause. It is generally recognized as death that occurs within 1 hour from the onset of cardiovascular symptoms. The four most common causes of SCD, which account for 50 percent of the morbidity in infants and children with congenital heart disease, are: congenital aortic stenosis, Eisenmenger's syndrome, cyanotic congenital heart disease with pulmonary stenosis or atresia, and hypertrophic obstructive cardiomyopathy. Less common causes include endocardial fibroelastosis, Ebstein's disease, myocarditis, congenital complete atrioventricular block, primary pulmonary hypertension, myocardial bridge and anomalous origin of the coronary arteries. Mitral valve prolapse is known to be associated with ventricular dysrhythmias and SCD. Postoperative congenital heart disease patients continue to have an increased risk of sudden death despite successful repair of the cardiac defect

Cardiac dysrhythmias account for many cases of sudden death in patients with congenital heart disease who have had surgery. Sudden death resulting from dysrhythmias also occurs in mutations that prolong the QT interval. Between 9-15 % of victims of sudden infant death syndrome carry a mutation for the long QT.

In children and teenagers, sudden death is a rare event. Approximately 20–25% of the deaths occur during sports. The majority of SCD at this age is due to arrhythmic causes.

The samples that should be taken at post mortem in a cardiac death include:

- Skin biopsy for fibroblast culture and genetic investigation

- Collection of myocardium, spleen and kidney samples to snap freeze in liquid nitrogen for potential DNA analyses
- Myocardium samples to snap freeze in liquid nitrogen for potential polymerase chain reaction studies for viral pathogens and histochemical staining.
- Blood and bile spot card for metabolic disease screening
- Myocardium and skeletal muscle samples for electron microscopy

26th August 2014 (Tuesday)
1330-1500
Kedah Room

Symposium 2: Update on biomarkers in the management of common cardiac emergencies

S2a. BNP in diagnosing heart failure. An experience in an emergency department in Malaysia

Mohd Idzwan Zakaria

Faculty of Medicine, University of Malaya, Kuala Lumpur, MALAYSIA

Abstract not available at time of printing.

S2b. Role of BNP in the management of acute and chronic heart failure

A Mark Richards

Cardiovascular Research Institute, National University of Singapore

The cardiac natriuretic peptides are of proven utility in the diagnosis, prognosis, monitoring and management of heart failure (HF). International guidelines endorse their use in assisting diagnosis of acute HF in cases of symptomatic (breathless) patients where the diagnosis may be otherwise unclear. Plasma BNP and NT-proBNP are independently prognostic and provide insights into risk stratification in all grades (A to D) of HF from asymptomatic community-dwelling patients who carry cardiovascular risk (such as hypertension or diabetes) but as yet have no abnormality of cardiac structure or function through to end-stage HF. Serial measurement of plasma B type natriuretic peptides (BNP or NT-proBNP) have also been demonstrated as useful in adding titration of treatment and application of this approach together with standard clinical care may reduce mortality and episodes of recurrent acute decompensated HF by ~ 20 % .

S2c. Cardiac biomarkers in ED chest pain

Swee-Han Lim

Department of Emergency Medicine, Singapore General Hospital; Yong Loo Lin School of Medicine, National University of Singapore; Duke-NUS Graduate Medical School Singapore

Accurate identification of the cause of chest pain is a challenge to the emergency physician because a significant proportion of patients with acute coronary syndrome (ACS) present atypically. The single or serial 12-lead ECG performed at the emergency department (ED) has a sensitivity of only 40-60% for acute myocardial infarction (AMI) or ACS. Cardiac troponins (cTn) are the most sensitive and specific biochemical markers of myocardial damage. High sensitivity troponins (hsTn) have been shown to have increased accuracy in the diagnosis of acute myocardial infarction (AMI), both at presentation and upon early onset of chest pain. However, hsTn levels may be elevated even in certain non-ACS settings. Identification of patients with unstable angina without AMI also remains a challenge, as the sensitivity of cTn in this area remains moderate to low. Whilst more than 85% of the patients presenting to the ED with chest pain are due to benign cases, there remain a few life-threatening causes of chest pain e.g. aortic dissection, pulmonary embolism, pericarditis, pneumothorax/pneumomediastinum, esophageal rupture. As these conditions are not commonly encountered in the ED, we should maintain a high degree of suspicion for them.

S2d. High-sensitivity troponins – Lessons from the laboratory

Tar-Choon Aw

Singapore Institute of Advanced Medicine, Singapore

Cardiac troponins (cTn) are vital in the evaluation of patients for possible acute coronary syndromes (ACS). Newer assays capable of detecting lower levels of TnT (Roche) in blood even in normal subjects have become available since 2010 and for TnI (Abbott) since 2013. There is increasing interest in the use of these biomarkers for ACS and other applications. The new cTn assays, termed high-sensitivity troponins (hs-cTn), have improved precision such that troponin levels at the 99th percentile upper reference limit (99PURL) can be measured with a precision of < 10% and that they can detect measurable amounts of cTn (above the assay's limit of detection) in over 50% of healthy individuals.

The distribution of circulating troponins is non-gaussian, hence a large number of subjects are required (at least 300, preferably 500) to mitigate against the distortionary effects of high-end outliers when deriving the 99PURL. Gender differences in cTn are increasingly recognized, with female values 35-50% lower. Should a single cut-point be used for hs-cTn is being debated. However, there is paucity of reference population studies with large enough subjects to accurately define sex-specific 99PURL – Gaggin. ClinChem 2014: hs-TnT (n=1157) and Aw. ClinChimActa2013: hs-TnI (n=1120). Undetectable hs-cTn values are observed in younger subjects especially females < 40 and their inclusion in reference range studies may lower the 99PURL (Aw ClinChem 2014). The 99PURL must be verified for each new hs-cTn assay but a large reference range study (if already available) is probably not needed.

Pre-analytical confounders include diurnal variation and non-ACS conditions. Neuromuscular disorders (e.g. muscular dystrophy) can cause elevations in TnT but not TnI. In fact the increased TnT in patients with hypothyroid myopathy and statin myositis can improve with resolution of their condition. A single hs-cTn result may not be sufficient for evaluation of ACS, hence serial sampling is needed. This is especially so in patients with impaired renal function who have elevated cTn in proportion to the eGFR including the many older subjects with chest pain presenting to the emergency department (Aw ClinChem2014).

In the analysis of cTn, hemolysis and fibrin clots are confounding factors to avoid. Besides, anti-troponin antibodies and macro-troponin can interfere. The assay time for hs-cTn on the main autoanalyzers is quite good (9 min hs-TnT and 18 min hs-TnI). With careful attention to sample delivery and their lab processes the central lab can provide a receipt-result time of 30-45 min. However, if turn-around times (TAT) are not acceptable the alternative is to use a point-of-care (POC) device with poorer limit of detection or even to provide a satellite lab at the care site. The ordering of a panel of cardiac markers (including CK-MB and CK) is not evidence-based and should be discontinued as they can impact TAT.

Result should be reported in units with whole numbers (ng/L preferred or pg/mL) and not in decimal points (ng/mL or ug/L) to avoid staff confusion and errors.

The new hs-cTn will usher in a new era of opportunities and we (clinicians and laboratorians) should seize them.

26th August 2014 (Tuesday)
1330-1500
Perak Room

Symposium 3: Enhancing microbiology diagnostics in Asia Pacific – moving forward

Chairpersons: Umi Kalsom Ali; Siti Norlia Othman

S3a. Perspective from Malaysia

Victor Lim

International Medical University, Kuala Lumpur, Malaysia

Infectious diseases remain an important cause of morbidity and mortality in Malaysia. There is a need to (a) improve clinical outcomes for patients with infections (b) enhance measures to control health-care associated infections (HAI) (c) detect and control emerging infectious diseases in a timely and effective manner (d) contain antibiotic resistance and improve antibiotic use.

The microbiology laboratory plays an important and crucial role in meeting these challenges. The microbiology services should continually improve its ability to diagnose infections, detect resistance and reduce turnaround times. More accurate and timely identification of pathogens and resistance would facilitate early and better management of infectious diseases leading to better clinical outcomes and more appropriate use of antibiotics. It would also enable earlier detection of HAI and allow for prompt and effective interventions to be put in place. In Malaysia the microbiology laboratory, in particular the consultant microbiologist is also expected to play a leadership role in infection control and antibiotic stewardship.

In Malaysia the laboratory diagnosis of bacterial infections is currently largely dependent on culture while the identification of bacteria is mainly through biochemical tests. Sensitivity testing is predominantly through disc diffusion tests and virological diagnosis is mostly through the use of serological tests. There is limited use of immunological and molecular biology techniques in routine diagnostics. These tests are highly operator dependent with marked inter-operator variability. The work is labour intensive and turnaround times are unsatisfactorily lengthy.

Over the past decade there has been tremendous progress in diagnostic capacity due to the development of new technologies like MALDI-TOF, microarrays and next generation sequencing. The use of these technologies increases the accuracy of diagnosis and resistance detection with much shorter turnaround times and in some instances at a lower cost.

There is a case to adopt these new technologies, at least in the major and reference laboratories in the country. There is a need to set up a network of laboratories that will work together in a harmonized and coordinated fashion. There is also a need for the laboratory based consultants to work and collaborate more closely with their clinical counterparts in the areas of clinical management, infection control and antibiotic stewardship. A national masterplan is required to bring together all the major stakeholders – Ministry of Health, universities and private sector to formulate strategies for microbiology diagnostic services in the country.

S3b. Perspective from Hong Kong

Margaret Ip

Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong SAR, CHINA.

Methicillin-resistant Staphylococcus aureus (MRSA) is a leading cause of bacterial infections both in healthcare facilities and in the community. A limited number of MRSA clonal lineages are responsible for the majority of epidemics worldwide and there is dynamic spread across the globe. Hospital-Associated MRSA (HA-MRSA) is still endemic in hospitals in Asia, including Hong Kong and Mainland China. Community-Associated MRSA (CA-MRSA) clones have been spreading rapidly in the community and also infiltrating healthcare facilities. Recent epidemiology studies indicate that we are meeting emerging challenges in the MRSA infection control: distinguishing between HA, CA- and livestock-associated MRSA (LA- MRSA) as they spread to new reservoirs, in order to monitor these changing trends of pandemic clones. For effective infection control and prevention, molecular typing is essential to aid interpret the epidemiological trends, to monitor transmission and detect genetic diversities of these strains so as to formulate strategies of control. Molecular typing methods focus on the establishment of rapid, non-culture, cost-effective methods at the local diagnostic laboratory level on one hand while to explore the genetic basis with accurate characterization and high discrimination on the other. Whole genome sequencing in clinical microbiology has revolutionized our understanding of MRSA in many aspects and provided insights about the genetic basis, such as in outbreak investigation, in evolution and phylogeographic distribution studies. Some of the recent work conducted will be presented.

S3c. Perspective from Australia

Raymond C Chan

Department of Microbiology, Sydney South West Pathology Service, Royal Prince Alfred Hospital, Camperdown, Sydney, Australia; RCPA QAP Pty Ltd, St Leonards, Sydney, Australia

The Asia-Pacific region comprises many countries, all from different backgrounds, with different health service structures and capacities and at different stages of economic development. The region faces significant challenges from infections, both established and emerging, and from increasing antimicrobial resistance.

Microbiology diagnostics are advancing steadily from point of care card tests to complex technologies requiring significant knowledge and service infrastructure for optimal delivery. Ensuring they are effectively used throughout the region to meet these challenges is complex and not necessarily simply served by mere uptake.

Significant gains in health outcomes may not even depend on their availability in some countries. For other infections, regional support and coordination for surveillance and building health service capacity will be more important.

27th August 2014 (Wednesday)
0830-1000
Sabah Room

Symposium 4: Molecular Pathology

Chairpersons: Sabariah Abd Rahman; Mohamed Rafie Md Kaslan

S4a. Next generation sequencing in cancer diagnosis

Roziana Ariffin, Nor Hidayah, Kamalru Azman

Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Next-generation sequencing methods are increasingly being adopted by molecular genetics lab worldwide. However implementing next-generation sequencing based test possess a major challenge for individual lab. In this context, international collaborative effort is important not only to ensure compliances of diagnostic standards but also to provide precious sequencing resources in characterization of any particular tumour. Our lab approach in integrating next-generation sequencing into clinical practice includes targeted genetic sequencing to detect mutation in genes of therapeutic importance. For these, we need to rapidly screen numerous genes at an affordable price. Following which we foresee the next-generation sequencing role in personalized monitoring of disease through detection of tumour DNA in peripheral blood of patient. Several issues with next-generation sequencing includes sequencing error rates which ranges from 0.1 to 10% or greater depending on sequencing chemistry and configuration, systematic bias based on approach, short sequence reads (<250 bases) and massive data output (data storage management and variant calling analysis). Ultimately although characterization of structural changes in the cancer genomes by next-generation sequencing will provide important pieces of knowledge, epigenetic changes, contributions from the tumour microenvironment and germline genetic variation will also have to be taken into account to have the full picture of the disease.

S4b. Molecular cytogenetics in ovarian neoplasms

Annie NY Cheung

Department of Pathology, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Ovarian tumours encompass a heterogeneous group of neoplasms based on their clinical, histopathological, and molecular features. The updated classification of ovarian tumours includes six major histological types: serous, mucinous, endometrioid, clear cell, Brenner and seromucinous. Each histological type is further divided into benign, borderline (or atypical proliferative). Undifferentiated carcinoma is referred to ovarian carcinoma with identifiable lineage. It is proposed that ovarian carcinomas can be distinguished into Type I and Type II tumours.

Type I tumours include mucinous, endometrioid and clear cell carcinoma, low grade serous carcinoma, borderline serous, mucinous and endometrioid tumours, as well as malignant Brenner tumour. They are associated with mismatch repair genes, *BRAF*, *KRAS*, *beta-catenin* and *PTEN* mutations. Low grade serous carcinomas are genomic stable though *BRAF* and *KRAS* mutations are common. *KRAS* mutations and *HER2* amplifications are usually exclusive events in mucinous carcinomas. Inactivation mutations of *ARID1A* and beta-catenin pathway are deregulated in about one-third of ovarian endometrioid carcinomas. *PIK3CA* and *PTEN* mutations are found in 20% of such carcinomas, sometimes concurrently. *ARID1A* mutation is the most common mutation identified in ovarian clear cell carcinoma (>50%). Type I tumours appear to develop progressively from cortical inclusion cysts or endometriosis to borderline tumours to invasive carcinoma.

Type II tumours, on the other hand, are all high grade tumours. They include high-grade serous carcinoma, undifferentiated carcinoma and malignant mixed mesodermal tumour (carcinosarcoma). *p53* mutations are commonly found. Inactivations of *BRCA1* and *BRCA2*, germline or somatic, are detected in significant portion of high grade serous carcinomas. In addition, chromosomal aberrations as well as amplifications or mutations of *PKI3CA, AKT, CCNE1* genes are also common.

In recent years, thorough examination of prophylactic salpingo-oophorectomies of genetically susceptible women with *BRCA1* and *BRCA2* mutations led to the recognition of clinically occult tubal carcinomas. Majority of these early carcinomas originate in the fimbriae which is also reported to be the origin of a significant portion of primary peritoneal serous carcinomas. Besides in-situ and occult invasive carcinomas, small linear p53 positive foci, which has been termed p53 signatures, has also been detected in non-neoplastic mucosa of the distal fallopian tube. Extensive embedding and examination of the fallopian tube from women with ovarian high grade serous carcinomas is therefore necessary

S4c. Era of molecular targeted therapy for lung cancer – The role of pathology

Manuel Salto-Tellez

School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland, UK

Traditionally, histopathologists have applied three main approaches to the molecular diagnostics of FFPE material: a) a collaborative role (adapting the histopathology practice in tissue handling and subsequent diagnosis to facilitate molecular testing performed by others); b) a leading role (actively running the laboratories that perform these tests within tissue pathology laboratories); or c) a detached role (neither actively nor passively involved in the use of tissue samples for subsequent molecular diagnostics). Accepting that option (c) is not valid any longer in modern pathology, this lecture will review the current standard-of-care tests applicable to lung cancer (EGFR and ALK), and those tests that would complement the therapeutic taxonomy of lung cancer (HER2, ROS1, KIF5B-RET, etc), and discuss the role of pathologists in options (a) and (b) above. Some aspects of this lecture have been reviewed in *Salto-Tellez - Overview of Molecular Tests and Personalized Cancer Medicine. In: Dongfeng Tan and Henry T Lynch, Principles of Molecular Diagnostics and Personalized Cancer Medicine, Wolters Kluwer Health, 2013* and in *Salto-Tellez et al J Thorac Oncol. 2011;6(10):1663-9.*

27th August 2014 (Wednesday)
0830-1000
Selangor Room

Symposium 5: Paediatric Forensic Medicine

Chairpersons: Nurliza Abdullah, Khairul Anuar Zainun

S5a. Shaken baby syndrome – Is it real or just a misdiagnosis?

Marta Cohen

Histopathology Department. Sheffield Children's Hospital, Sheffield, UK.

The term "*Shaken baby syndrome*" (SBS) refers to the presence of the "*triad*" of: encephalopathy, retinal haemorrhage and subdural haemorrhage (SDH), usually in a young infant, who is under the care of an adult. The controversy about SBS is not whether an infant can be killed or severely injured by violent shaking. The controversy is centred on the specificity of the triad as a marker of SBS/non-accidental/abusive head injury. The term "whiplash shaken infant syndrome" was initially used by Caffey in 1974 to describe those cases where intracranial injury was present in the absence of external signs of head trauma. In 1972 Guthkelch had suggested that the bleeding came from the stretching and tearing of bridging cortical veins, which rupture into the subdural 'space' during the supposed shaking of the infant. Guthkelch's concept regarding the etiology of the subdural bleeding in SBS then became widely accepted. More than 40 years after Guthkelch's description, recent studies demonstrated many flaws in the origin, location and aetiology of the thin film bleeding in cases of alleged SBS: 1. There is no naturally occurring subdural space, whether virtual or real. Rather, the subdural 'space' is the result of a pathological process that tears open the weak dural border cell layer between the arachnoid and the dura; 2. Most of the trajectory of the bridging veins is in the subarachnoid space and 3. There is a rich vascular plexus in the dura, which becomes a good candidate to be the source of the thin film SDH. Not infrequently this is seen in cases of non-traumatic hypoxic-ischaemic encephalopathy, particularly in young infants with complex medical illnesses. These indicate that the SDH characteristic of the triad is an unreliable evidence of SBS. Therefore, a more appropriate term would be ''retino-dural hemorrhage of infancy'', recently coined by Guthkelch.

S5b. Non-accidental head injury from the clinician's viewpoint

Irene Cheah Guat-Sim

Department of Paediatrics, Paediatric Institute, Kuala Lumpur, Malaysia

More than 80% of the deaths from head trauma in children below the age of two are from non-accidental head injuries (NAHI).

It is important to have a high index of suspicion for NAHI as the presenting complaints are usually non-specific and a correct diagnosis is important to prevent death or morbidity. Neuroimaging should also be done in high risk abused children such as those with rib fractures, facial injury, multiple fractures and any physical injury in a baby aged below 6 months, even if they are without any signs of abnormal neurological findings to exclude occult head injury.

NAHI has to be considered when there is no history of trauma to cause head injuries with or without subdural haemorrhage. Once suspected, a careful evaluation should be done to identify supporting indicators of abusive head injury whilst investigations are being carried out to exclude other organic causes. Differential diagnosis of subdural haemorrhage and retinal haemorrhages include birth trauma usually in the first month of life, coagulopathies, congenital vascular malformation and metabolic disorders.

Other indicators of NAHI are extracranial injuries such as fractures or facial bruising, history discrepant with the clinical development of the child or severity of injury, and the presence of severe retinal haemorrhages. Clinical features and social risk factors which help differentiate between non-accidental and accidental cases will be discussed.

Reporting to child protection services and police should be done by clinicians once the possibility of NAHI is considered to ensure the child's future safety and to counsel the parents on how to handle prolonged crying in their child or choose a different child care option, and criminal prosecution where there is sufficient proof of abusive action.

27th August 2014 (Wednesday)
0830-1000
Kedah Room

Symposium 6: Transfusion & Transplantation

Chairpersons: Ainoon Othman, Kuperan Ponnudurai

S6a. Improving blood safety

Veera S Nadarajan

Department of Pathology, University of Malaya, Kuala Lumpur, MALAYSIA

Blood transfusion has inherent immunological and infectious risks, considering that it involves the transfer of biological material from one individual to another. The discovery of the ABO blood group by Karl Landsteiner in 1900, laid the foundation for our current extensive but still limited understanding of the immunological characteristics of red cells, platelets, leucocytes and plasma proteins. As of date, thirty-four red cell blood group systems are identified by the ISBT, the molecular basis of which has already been elucidated. In addition, the molecular basis of many of the HPA, HNA and HLA antigens, which are expressed on platelets, neutrophils and lymphocytes are also known. Current technological advances, particularly in the field of molecular biology and genomics , has shifted the matching of donor and recipients at the serological level to a molecular level. This is already prevalent with regards to organ and stem cell transplantation, involving HLA matching. Red cell matching using molecular techniques however has several pitfalls, and would likely still remain supplemental to serological matching within the routine transfusion laboratory. Steps therefore must be in place to ensure that serological testing is done accurately by trained personnel within accreditated facilities. Automation and computerization has facilitated improvements in these laboratory processes. Nevertheless, molecular typing will have a strong presence in certain patient groups such in the difficult to transfuse patients having multiple antibodies or in the selection of rare combinations of blood groups, which ultimately should lead to better transfusion response and reduced incidence of transfusion reactions, while maintaining cost effectiveness.

Despite the remarkable advances in technology and improvement of blood safety in terms of immunologically-mediated and infectious risks, patients continue to suffer from significant morbidity and mortality resulting from transfusion, especially within developing countries. While transfusion associated hepatitis and HIV have nearly been eliminated in the high-development index countries with the introduction of sensitive nucleic acid based infectious disease screening, many countries still lack the infrastructure, logistics and funding for such technologies, let alone to conduct standard serological screening and recruitment of safe volunteer donors. New strategies to recruit safe donors as well as screen blood efficiently in resource limited conditions have been proposed and should contribute to significant improvements in blood safety.

The multi-pronged approach to transfusion safety, involving safe donor recruitment and retention, effective blood screening, blood processing, pre-transfusion testing as well as intelligent use of automation and computerization has currently made blood transfusion one of the safest possible medical interventions, at least in developed countries. There is still much work to be done in medium and low-development index countries, which however should be resolved as long as there is commitment by all involved stakeholders.

S6b. Clinical utility of genotyping red blood cell antigens

David S Wilkinson

Virginia Commonwealth University, Richmond, VA, USA

Red blood cell (RBC) phenotyping is an important part of the laboratory workup of certain types of patients requiring transfusion. Traditionally, RBC phenotyping was accomplished with serological methods. However, there are many limitations to these methods, such as unavailability of specific antisera, expensive reagents, labor intensity and subjectivity of the results. Certain clinical situations preclude or complicate accurate phenotyping by serological methods, including recent transfusion and a positive direct antiglobulin test (DAT). Developments in DNA-based methods have brought genotyping RBC antigens, and hence the accurate prediction of phenotype, within the reach of most hospital laboratories. One platform, the BioArray™ HEA BeadChip™, is a DNA-based system that tests for a multiple single nucleotide polymorphisms (SNP) that are responsible for variations in RBC antigen expression. The system utilizes a multiplex PCR reaction to amplify the target DNA of interest and elongation mediated multiplexed analysis of polymorphisms to identify 24 polymorphisms associated with 38 RBC antigens and phenotypic variants in a single test. Genotyping is especially helpful in patients with warm autoimmune hemolytic anemia, antibodies to high frequency antigens, alloantibodies due to recent transfusion, and frequently transfused patients with multiple alloantibodies. As the genotyping technology matures and becomes more widely deployed, we may see the day when all donor units and donors will be genotyped, allowing complete antigen matching of transfused RBC.

S6c. Role of pathologists and laboratory in the management of organ donor

Fadhilah Zowyah Lela Yasmin Mansor

National Transplant Resource Centre

Transplantation is well established to be the best therapeutic option for patients with end-stage organ failure. However due to the chronic shortage of organs in the presence of ever increasing demand for transplants, more and more marginal donors are being used as source of the organs and tissues. The pathologist and the laboratory play a very important role in the management of the deceased donor to ensure the safety and quality of the organs transplanted, in ascertaining that the donated organs are free from transmissible infections and diseases and organ function still viable. The laboratory investigations, be it biochemical, haematological, microbiological, virological and histopathological will need to be done urgently and expedited with reliable fast and verified results to assist the clinician looking after the brain dead donor to evaluate suitability, maintain organ function and match the donor immunologically to the waiting recipients. When the donor is very marginal, more investigations will be required which may be outside the standard protocol but still need to be done urgently. The pathologist should be involved in the discussion and his or her expert opinion considered in the decision whether to accept the donor or not. The laboratory should also store a serum specimen of the donor for a specified period of time so that any untoward findings or infections in the recipients can be tested to see if it came from the donor. Finally the forensic pathologist can expedite and facilitate any post mortem required and issue the report to the deceased family.

To facilitate and expedite the laboratory investigations, a pathologist and laboratory personnel are included in the Tissue Organ Procurement (**TOP**) teams that have been set up in MOH hospitals to manage the deceased donors.

27th August 2014 (Wednesday)
0830-1000
Perak Room

Symposium 7: Renal Medicine

Chairpersons: Tar-Choon Aw, Hapizah Mohd Nawawi

S7a. Pathophysiology of endothelial damage and chronic kidney failure

Roberto Verna

Center for Sport Medicine and Management; Department of Experimental Medicine - Faculty of Medicine, University of Rome, Italy

The endothelium is a physical barrier that separates ultrastructurally components of the vessel wall and the contents of the vessel lumen. This barrier allows the movement of solutes small rather than large molecules, and thus is involved in self-regulation of the tissues, regulating cellular trafficking of nutrients. The vascular endothelium determines the activities, maintains the fluidity of blood, contributes to the balance between local mediators pro-and anti -inflammatory as well as between procoagulant activity and the anticoagulant. Finally, the endothelium participates in angiogenesis, ie the generation of new blood vessels, interacts with the circulating cells, mediates the adhesion of platelets and leukocytes to the vessel wall in case of wounds and inflammation, respectively, and undergo cell death programmed. Each of these activities is regulated differentially for both the position and for the time, a phenomenon that has been called diversity or heterogeneity of vascular endothelial cells. The endothelial cells are a heterogeneous population, their phenotypes are determined by their embryonic origin (macro - or microvascular) and by local environmental factors. Specialized functions of the endothelium may be that is anatomically specific, as occurs in the glomeruli.

Since the discovery in 1980 by Furchgott and Zawadzki, that acetylcholine requires the presence of endothelial cells to cause vasodilation, there have been tremendous advances in our understanding of the biology of endothelial cells. Now, we know that this is largely the result of the vasodilator nitric oxide derived from the endothelium, and to a lesser extent prostacyclin, endothelium derived hyperpolarizing to various factors, the type natriuretic peptide C. In addition, the endothelium secretes various vasoconstrictor substances such as thromboxane A2, endothelin, angiotensin II, reactive oxygen species. Modulators of inflammation include adhesion molecules such as ICAM- 1 (intercellular adhesion molecule - 1), VCAM-1 (vascular adhesion molecule - 1), E- selectin, nitric oxide and nuclear factor kB (NF- kB). Hemostasis is modulated by the endothelium through the release of plasminogen activator (t-PA), its inhibitor (PAI -1), and von Willebrand factor (vWF), nitric oxide, prostacyclin, thromboxane A2 pathway inhibitor tissue factor (TFPI), fibrinogen.

The layer of endothelial cells is the "guardian" of molecular traffic between the blood and the surrounding tissue, and endothelial integrity plays a fundamental role in many aspects of vascular function: for example, the control of vasomotor tone and permeability.

Cardiovascular risk factors such as hypertension can cause endothelial dysfunction and even disintegration, resulting in the disappearance of the small vessels (vascular rarefaction) and tissue hypoxia. In patients with chronic kidney disease (CKD), ongoing endothelial damage in the capillary system of the renal medulla and vascular rarefaction that accompanies the processes are thought to be central to the progressive renal damage.

In the case of kidney failure, endothelial dysfunction and atherosclerosis are almost always present, as well as cardiovascular complications. Lindner has called attention to the excessive incidence of atherosclerotic cardiovascular mortality in uremic patients on hemodialysis.

Endothelial cell damage or injury are invariably associated with clinical conditions such as thrombosis, hypertension, renal failure and atherosclerosis, and may also be responsible for accelerated atherosclerosis in patients with chronic renal failure. The traditional risk factors cannot explain the

high prevalence and incidence of cardiovascular disease in chronic kidney disease, so they must be studied other non-traditional risk factors such as endothelial dysfunction, oxidative stress and insulin resistance.

S7b. Creatinine standardisation: Pilot group results of the Mexican task force on chronic kidney disease (CKD)

Laura Cortés Sanabria[1]; Alfonso Cueto Manzano[1]; Guillermo García García[1]; Héctor Ramón Martínez Ramírez[1]; Gisela Mercado Salgado[1]; Roberto Ruiz-Arenas[1]; David Seccombe[2], and Rosa Isabel Sierra Amor[1]

[1]Alianza Mexicana para Prevenir las Enfermedades Crónicas, A.C.(AMPEC). México.
[2]CEQAL Inc., Vancouver, Canada

Introduction: CKD is a major public health problem worldwide. In Mexico, a national end-stage renal disease registry has not been developed. However, data from single state registries and from the US Renal Data System indicate that some Mexican states have an unusually high incidence and prevalence of CKD. Kidney function is estimated by calculating glomerular filtration rate using serum creatinine (Cr) and one of several equations. Since extensive variation of Cr determination is common among different clinical laboratories (CLs), standardization of Cr determination is critical for diagnosis/management. We present the baseline assessment of Cr determinations across few CLs in Mexico. *Materials and methods:* CLs nationwide were invited to participate via survey. Selected CLs received 3 sets (3 samples/set) of human serum samples (matrix insensitive, commutable) sent from a reference CL in Canada. Different Cr concentration within samples correlated with the diagnosis of CKD stage 3. CLs recorded their Cr determinations on each sample (3x/sample), the methodology, and the manufacturer used. Intra and inter-run coefficient variation (CV) as well as total error percentage (TE%) were calculated and used for comparison. *Results:* A total of 17 CLs, 5 from public and 12 from private sector participated voluntarily. The mean CV% was 4.56 (1 to 18.04 %) and mean TE% was 16.63 (3.91 to 47.93 %). When grouped, public CLs had a mean CV% of 3.93 and a mean TE% of 18.98, and private CLs of 4.82 and 15.66, respectively. When compared individually to international standards, 4 CLs had a "minimum acceptable performance" (≤11.4 TE%), 3 a "desirable performance" (≤7.6 TE%), and 10 an "undesirable performance" (between 13.41 and 47.93 TE%). None had an "optimum performance" (≤3.8 TE%). *Discussion:* The baseline assessment of the program illustrates a great disparity among CLs in Mexico and reflects the urgency to develop a nationwide standardization program.

S7c. GFR estimating equations in mixed ethnic Asian populations

Sunil Sethi

Department of Laboratory Medicine, National University Health System, Singapore

Renal disease is common and often co-exists in patients with other disorders of cardiovascular and metabolic origin. There is a need for early detection and monitoring of patients with renal injury. Biomarkers play a vital role in the diagnosis and monitoring of chronic kidney disease. Recently, novel serum and urine biomarkers appear to provide early indication of acute kidney injury. The currently available repertoire of renal biomarkers include urine albumin, creatinine, cystatin C and neutrophil gelatinase-associated lipocalin (NGAL). With advances in assay standardization and recommendations in clinical practice guidelines several serum creatinine-based equations have been developed to estimate the glomerular filtration rate (GFR). These include the Cockroft and Gault, modification of diet in renal disease (MDRD)and Chronic Kidney Disease Epidemiology Collaborations (CKD-EPI) equations. It is recommended that the method of calculating eGFR should be CKD-EPI formula, and that all laboratories should report eGFR values as a precise figure to at least 90mL/min/1.73m^2. Routine calculation of eGFR is not recommended in children and youth, or in pregnant women. Serum creatinine concentration (preferably using an enzymatic assay for paediatric patients) should remain as the standard test for renal function in these populations.

27th August 2014 (Wednesday)
1445-1645
Sabah Room

Symposium 8: Gynaecology and Perinatal Pathology

Chairpersons: Hayati Abd Rahman, Geok-Chin Tan

S8a. Molecular cytogenetics of trophoblastic diseases

Annie NY Cheung

Department of Pathology, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Gestational trophoblastic disease (GTD) represents a family of trophoblast disorders. Besides the overtly malignant tumors choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor, GTD also includes the potentially malignant complete and partial hydatidiform moles, invasive moles and non-neoplastic extravillous trophoblastic lesions: exaggerated placental site, placental site nodule and nodule as well as abnormal (nonmolar) villous lesions.

Molecular cytogenetic studies, besides enhancing our understanding of this complex family of diseases, also facilitates diagnosis and management. Various laboratory techniques including microsatellite analysis, flow cytometry, in situ hybridization, sequencing, comparative genomic hybridization, and imprinting gene studies have been applied.

Extensive use of ultrasound in early pregnancy has given rise to increased diagnostic dilemma, particularly the differential diagnosis of early complete mole, partial mole and abnormal nonmolar villous lesions. Previous studies have demonstrated the issue of interobserver variation in such diagnoses. Vast majority of complete moles are diploid and purely androgenic while most partial moles are triploid having excessive paternal genome with maternal contribution. Adjunct techniques, such as $p57^{Kip2}$ immunohistochemistry as well as ploidy and microsatellite analysis, have become more commonly applied to facilitate diagnosis of GTD. However, we should be understand clearly the diagnostic expression pattern and limitation of such tests to avoid misinterpretation.

Such genotyping techniques are also useful in diagnosis of rare scenarios such as a twin pregnancy with one normal twin and one complete mole, placental mesenchymal dysplasia and familial biparental complete moles. The latter develops as a result of abnormal imprinting with mutations of NALP7/NLRP7 gene. Molecular cytogenetic studies are also useful in distinguishing gestational and non-gestational trophoblastic choriocarcinoma, which are treated with different chemotherapy regime.

We should still bear mind the basic prerequisite of processing adequate or all evacuated material for histopathological evaluation as well as correlation with clinical, radiological and biochemical findings. If ancillary techniques are not available or helpful, a report may be issued stating the most likely diagnosis and the reasons for uncertainty. The integrated approach will be useful to minimize the risk of missing preventable or treatable gestational trophoblastic neoplasia or overdiagnosis causing unnecessary investigation and treatment.

S8b. Perinatal autopsy

Teck-Yee Khong

SA Pathology, Women's and Children's Hospital, North Adelaide, Australia
University of Adelaide, Australia

Each autopsy is unique and personalized to the deceased and, in the perinatal period, the findings are also extended to other family members. It remains the gold standard in diagnostic evaluation of the causes of perinatal death and helps in understanding the events surrounding the death and may help in future pregnancy planning by enabling consideration of recurrence risks and different management strategies. World-wide, there are about 2.6 million stillbirths, defined as a fetal death of 500 g or more, and about 3.8 million neonatal deaths, defined as death of a newborn before 7 days of age, annually. In addition to these perinatal losses, there are also fetal losses because of therapeutic terminations following antenatal diagnosis, fetal deaths under 22 weeks' gestation and newborns that live past 7 days because of advances in neonatal intensive care. Despite this, most are not investigated. Even in high income countries, many are either not investigated or under investigated, mainly because of consent, workload and cost issues, despite evidence that an autopsy can change or reveal a new diagnosis or provide additional findings in between 22 – 76% of stillbirths, neonatal deaths or terminations following antenatal diagnosis. Cases will be presented to illustrate various aspects of the usefulness of the perinatal autopsy: finding an accurate cause of death, excluding some causes of death, identifying disorders with implications for counselling and monitoring for future pregnancies, assisting in the grieving process, obtaining tissues for genetic tests, fostering research, informing clinical audit of perinatal deaths, confirming antenatally diagnosed or suspected fetal pathology; teaching pathologists and medical students; and providing evidence for medicolegal reasons

S8c. Endometrial pathology – an update

Annie NY Cheung

Department of Pathology, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Endometrial cancer is a common gynaecological cancer worldwide. There are two major types of endometrial cancer exhibiting different genetic and clinicopathological features. About 80% of endometrial cancers show endometrioid differentiation and are designated as type I carcinomas. They are often preceded by endometrial hyperplasia related to excessive oestrogenic stimulation. Type II carcinomas are poorly differentiated or of non-endometrioid differentiation (serous or clear cell types). They are not oestrogen driven, often arise in a background of atrophic endometrium and exhibit more aggressive clinical course.

The endometrial hyperplasia schema is currently the most widely used classification system for premalignant lesions of type I endometrioid adenocarcinoma. A two tier system of endometrial hyperplasia, atypical hyperplasia and hyperplasia without atypia, is adopted in the new WHO classification. Distinction of the architectural pattern, simple or complex, is no longer considered necessary. Endometrioid For type II uterine serous carcinoma, serous endometrial intraepithelial carcinoma refers to precursor lesions to uterine serous carcinoma. Intraepithelial neoplasia (EIN) is included as an alternative term for atypical hyperplasia, using the same diagnostic criteria. It is worth noting that the term "endometrioid" is used for "E"IN to reflect its status as precursor to endometrioid carcinoma.

A new category of neuroendocrine tumour has been introduced. This includes low-grade neuroendocrine tumour (or carcinoid tumour) as well as high-grade neuroendocrine carcinoma which can further subcategorized into small cell and large cell neuroendocrine carcinomas.

Under the category of mixed carcinoma, the minimum percentage of the second component has been reduced from 10% to 5% in the recent version. This is because of the belief that even the presence of 5% of serous carcinoma can adversely affect the prognosis. In addition to undifferentiated carcinoma, dedifferentiated carcinoma refers to the coexistence of undifferentiated carcinoma together with FIGO grade 1 or 2 endometrioid carcinoma. Understanding the different categories of endometrial carcinoma and their precursor lesions will enable timely diagnosis and therapy. Adequate sampling and thorough histopathologial evaluation with appropriate help of immunohistochemical and molecular techniques are crucial in diagnosis of this evolving and challenging field.

S8d. Placental pathology

Teck-Yee Khong

SA Pathology, Women's and Children's Hospital, North Adelaide, Australia
University of Adelaide, Australia

Despite the placenta being the body's largest biopsy, surgical pathologists generally fail to understand the importance of its examination. Some of this misunderstanding comes from the lack of familiarity with the pathological lesions and their definitions, the relationship between presence or absence of lesions with clinical outcomes and the mistaken belief that there is little value in placental examination. Guidelines based on best currently available knowledge provide indications for placental examination, which can be categorised as being maternal, fetal or placental. Studies have shown that in tertiary centres, between one-half to two-thirds of placentas are not examined when they should have been. Surgical pathology reporting of placentas is no more difficult than for any other organ: a careful gross examination and selection of representative blocks of normal-appearing and lesional areas followed by a systematic topographic histological approach should allow all pathological findings to be documented. These findings need to be placed in the clinical context with a commentary that should include recurrence risk. Potentially recurrent placental lesions include chronic histiocytic intervillositis, chronic villitis of unknown aetiology, placenta accreta, fetal artery thrombosis and massive perivillous deposition.

27th August 2014 (Wednesday)
1445-1645
Selangor Room

Symposium 9: Personalised diagnostics in infectious diseases

Chairpersons: Sahlawati Mustakim, Zalina Ismail

S9a. Respiratory infections

Margaret Ip

Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong SAR, CHINA.

Pneumococcal disease continues to be a challenge worldwide despite the availability of effective vaccination. However, the focus of research in relation to pneumococcal disease has changed priorities somewhat with the introduction of vaccination.

Key areas of interest in the post conjugate vaccination era include serotype replacement in colonization and disease, effect on other bacterial pathogens in the nasopharyngeal niche, viral and bacterial interactions in respiratory disease, continuing antimicrobial non susceptibility, and pneumococcal disease among adults.

Hong Kong SAR is in the unique position of being one of the first and few Asian regions to have introduced conjugate pneumococcal vaccination in the childhood vaccination programme. An update on the current status and diagnostics used in the study of pneumococcal disease and carriage will be presented.

S9b. Malaria infections

Rohela Mahmud

Department of Parasitology, Faculty of Medicine, University of Malaya, Kuala Lumpur

Malaria is caused by the protozoan parasite of the genus *Plasmodium*. Malaria parasite include species that infect mammals, rodents, reptiles and birds. Humans are infected by five species of malaria parasite namely *Plasmodium falciparum, P. vivax, P. malariae, P. ovale* and *P. knowlesi. Plasmodium falciparum* causes the most serious and fatal type of malignant malaria. *Plasmodium vivax* is the most prevalent and widely distributed species. Malaria caused by *P. vivax, P. malaria* and *P. ovale* generally cause benign malaria. *Plasmodium knowlesi* which is a simian parasite is the fifth species of human malaria. It has been recently found to infect humans in Southeast Asian countries including Malaysia and the infection can be fatal. Malaysia is endemic for malaria, particularly in the forested, hilly and under developed interior areas of Sabah, Sarawak and Peninsular Malaysia. The clinical diagnosis is based on the history, symptoms and clinical findings and must always be confirmed by a laboratory diagnosis. Laboratory diagnosis of malaria involves identification of malaria parasite or its antigens/products in the blood of the patient. Microscopy is gold standard for laboratory confirmation of malaria. There are limitations and challenges in using microscopy as a diagnostic method as seen in low parasitaemia, mixed infection and species misidentification. Microscopically *Plasmodium knowlesi* is commonly misidentified as *P. malariae*. The blood stages are morphologically similar on microscopy. The diagnosis of *P. knowlesi* in humans may be missed by microscopy since the early blood stages of *P. knowlesi* morphologically resemble *P. falciparum,* the mature blood stages and gametocytes are similar to those of *P. malariae.* Accurate malaria diagnosis requires adequate techniques, training and experience to avoid misidentification which could lead to wrong diagnosis and management. Antigen detection and

molecular methods have been developed and described as sensitive and specific methods for diagnosis of malaria parasites. Rapid and inexpensive laboratory methods are needed for accurate diagnosis and appropriate treatment of malaria.

27th August 2014 (Wednesday)
1445-1645
Kedah Room

Symposium 10: Quality & Training in Medical Laboratory

Chairpersons: Howard Morris, Johnson Stanslas

S10a. ISO15189:2012: New guidelines

Panadda Silva

Abstract not available at time of printing.

S10b. External QAP : Uncertainty of measurement

Peter Stewart

Abstract not available at time of printing.

S10c. Quality assurance – Valuable in surprising ways

Raymond C Chan

Department of Microbiology, Sydney South West Pathology Service, Royal Prince Alfred Hospital, Camperdown, Sydney, Australia; RCPA QAP Pty Ltd, St Leonards, Sydney, Australia

Quality Assurance is a fundamental component of successful and effective pathology laboratory activity. For many, it remains synonymous with proficiency testing.

However, this session will demonstrate that quality assurance is being construed much more broadly. Examples of activities that have occurred within Australia will be discussed such as total quality packages, non-analytical quality and high-level review of laboratory accreditation performance.

Expectations of laboratories are being set ever higher. Laboratories must be prepared for these evolving standards.

S10d. RCPA training programs

Tony Landgren

Board of Education and Assessment, Royal College of Pathologists of Australasia

The Board of the Royal College of Pathologists of Australasia following extensive consultation with Fellows, Trainees, Government, Industry and the Community have approved and substantially resourced implementation of a broad range of new and expanded programs designed to increase support for specialist professional practice in pathology and related disciplines. These changes include a substantial increase in the number of Fellows through the Faculty of Science and engagement within the forensic world of Clinical Forensic Medicine Practitioners and Forensic Odontologists.

Certification of continuing competency post award of a specialist qualification is a significant challenge for health profession representative bodies and the Royal College of Pathologists of Australasia has committed to developing programs that meet the needs of Fellows and have evidence supported credibility in the context of the increasing expectations of Governments, Employers and Communities.

This presentation will include eligibility criteria, organisational arrangements and program details in the following areas:

New College Faculties
Faculty of Clinical Forensic Medicine

Expanded Faculties
Faculty of Science
Faculty of Oral and Maxillofacial Pathology (Including Forensic Odontology)

New Training Programs and Qualifications
Multidiscipline Pathological Science - Fellow Faculty of Science
Forensic Odontology - Fellow Faculty of Oral and Maxillofacial PathologyClinical Forensic Medicine - Fellow Faculty of Clinical Forensic Medicine
Dermatopathology - Diploma of Dermatopathology

Training Program and Assessment Changes

Continuing Professional Development Changes

27th August 2014 (Wednesday)
1445-1645
Perak Room

Symposium 11: Innovative Devices and Tests

Chairpersons: Lai-Meng Looi, Tengku Norita Tengku Yazid

S11a. Cardiac devices

Jagdish Butany

University of Toronto, Canada

Cardiovascular disease remains the most significant cause of mortality and morbidity, all over the world. Its effective treatment is now a combination of pharmacotherapy and prosthetic cardiac devices (PCD). The earliest devices were rather crude prosthetic heart valves(PHV). Today there is a vast array of sophisticated devices that are implanted surgically into or onto the heart, with the nett result of improved quality of life, reduction in the incidence of sudden unexpected death, decreased hospital visits and increased life expectancy. These devices range from the "now" ubiquitous coronary stents to implantable half hearts and "immersible/intravascular " cardiac assist pumps.

Some of these devices, may malfunction, or even fail after a while, sometimes catastrophically. It is incumbent on the pathologist to examine these explanted devices, document the findings and report them to the appropriate authorities, so that improvements may be made.

At the end of this session, you should have an appreciation of some of the common devices, appreciation of how they fail and how to examine/ document the findings.

S11b. Morphological indexing system for fibrosis assessment using stain-free imaging and feature quantification algorithms

Dean Tai

Managing Director and Chief Scientific Officer, HistoIndex Pte Ltd, Singapore

Background: Digital pathology has advanced rapidly and the pattern recognition algorithm has been widely used to aid morphology-based diagnosis using digital imaging technologies in recent years. However, these methods are limited by issues such as staining-artifact and the constraint of 2D visualization from sliced tissue specimen, etc. *Methods:* By using stain-free imaging technics such as multi-photon and multiharmonic imaging microscopy systems, we obtained highly quantitative and reproducible images by direct protein detection, physical structural patterns recognition, and detecting other optical signatures without the need of any staining. These imaging techniques also provide 3D imaging capability without the need to physically slice the tissue samples. In addition, we developed feature-specific quantification algorithms to monitor fibrosis progression such as for portal expansion and bridging. We created indexes for these morphological features and later a combined index. We tested the imaging system and the combined index analysis on TAA model with male Wistar rats (n=25) and HBV patients (n=120), and compared the results with Metavir staging, FibroScan results, and various biochemistry markers and CPA (collagen proportionate area), etc. *Results:* Combined index approach showed a significant improvement in differentiating early stages fibrosis. The ROC for differentiating stages 0v1 is 0.92, comparing to 0.82 using CPA measurements. In addition, we found that certain indexes are more sensitive for differentiating certain stages of fibrosis development. For example, ROC for portal index (measures portal expansion) is highest between stages 1v2 (0.95); ROC for septal index (measures bridging fibrosis) is highest between stages 2v3 (0.99). *Conclusions:* By using the

stain-free imaging system, we obtained accurate quantitative measurement of the collagen progression. We also developed feature-specific quantification algorithms using images obtained with the stain-free imaging technique. We have verified the effectiveness of fibrosis assessment of this combined index approach in both animal and human fibrosis models. The results showed great improvement in early fibrosis detection, as well as the overall accuracy for fibrosis assessment. Furthermore, the technique can be expanded into 3D readily as the imaging system features 3D imaging capability, without the need of physical slicing and staining. We believe our study showed a new perspective for advancing digital pathology.

Objectives: To understand the advantage of non-stain imaging and the morphological indexing approach. In addition, to be able to combine these techniques for better fibrosis assessment.

S11c. The role of mass spectrometry in laboratory medicine

Dobrin Svinarov

Alexander Hospital, Medical University of Sofia, Bulgaria

There is an extraordinary flood of new technologies in pathology nowadays - sophisticated diagnostics based on mass spectrometry, genome assays and cell sorting platforms are driving the technological transfer and promote entrance of personalized medicine in clinical practice. The expanding role of mass spectrometry in laboratory medicine is based on dramatic improvement of analytical instrumentation coupled to adaptive and vigilant bioinformatic pattern-recognition tools. Mass spectrometry analysis of nucleic acids, proteins, peptides, and low molecular metabolites provides dramatic advantages: unbeatable specificity, extreme sensitivity, and high throughput: simultaneous analysis of multiple components in several minutes in a drop of blood. This technique could be viewed as a major tool for analysis of the clinical chemome, and as a clinical chemistry analyzer of the near future. In addition to classic application in specific fields like therapeutic drug monitoring of immunosuppressants, antiretroviral drugs, antidepressants, antipsychotics, and clinical toxicology, triple quadrupole LC-MS/MS provides unique selectivity and sensitivity in endocrinology for steroid profiling, analysis of testosterone, FT3 and FT4, screening of pheochromocytoma, assessment of vitamin D status; newborn screening for acylcarnitines, amino acids, steroids; analysis of angiotensins, oxytocin, ADH, hepcidine, and many newer biomarkers. Typical yesterday-research-based mass spectrometry platforms like Q-TOF, MALDI-TOF and Orbitrap are becoming routine diagnostic instruments in microbiology, and clinical proteome and peptidome assays. There is an ultimate demand for clear understanding of the development stages between discovery, selection and validation of newer biomarkers, as well as analytical method development and validation of mass spectrometry techniques that are standardized to meet criteria for clinical use with post validation routine proficiency testing assessment. Facing and resolving those challenges will open the way to ”omics” diagnostics and personalized management in clinical medicine, and will change our understanding of health and disease, assessment of risk, and prevention.

S11d. The thrombin generation test

Michael Laffan

Department of Haematology, Imperial College London, UK

The widespread application of the thrombin generation test (TGT) derives from the introduction of a fluorogenic substrate for thrombin by HC Hemker in the 1990's. This allowed continuous real-time thrombin measurement without repeated subsampling. Additional technical developments included corrections for the inner filter effect and for the effect of alpha 2- macroglobulin. Corn trypsin inhibitor can be added to block activation via the contact activation system, especially when low initiating concentrations of tissue factor are used. The effect of re-calcification remains controversial.

Despite some technical limitations the TGT has found wide applicability in numerous clinical and basic laboratory studies. However, differences in practice led to variation in results and these have not yet been standardised to a point where it can be used in clinical service.

The test is usually run using PPP or PRP. After initiation, there is a lag phase during which very low levels of thrombin are present. At the end of the lag phase factors V and VIII have become activated and the propagation phase begins during which there is rapid thrombin generation. This then peaks and neutralisation by antithrombin results in a fall in thrombin concentration back to base line. Most attention has focused on the area under the thrombin curve or 'endogenous thrombin potential' (ETP). This is largely because conventional clotting times such as the PT and APTT correspond only to the 'lag phase' of this process. Thus the TGT offers a much more complete and more extensive view of the coagulation process.

The TGT can be applied to investigate the coagulant capacity of plasma in different patient groups, such as those taking the COCP, or it can be used in a research setting to investigate the contribution of individual factors or processes to thrombin generation.

S11e. Toward quantitative, automated & Multiplexed solutions for tissue biomarker discovery & clinical translation

Mark Dupal

Perkin Elmer Inc.

Simultaneous quantitation of 4 or more biomarkers in intact tissue specimens holds the key to many questions in the biological basis of health and disease. However, reliable detection remains elusive due to technical challenges from many sources including antibody cross reactivity, difficulty in balancing signals from rare and abundant targets, tissue autofluorescence and interference between fluorophores, especially for co-localized targets.

Mark Dupal presents Opal™ and Vectra, a practical combination for highly multiplexed tissue biomarker imaging and analysis that addresses many of these challenges. Opal is an iterative process that incorporates the following:

- highly specific and reproducible results
- eight or more biomarkers may be imaged simultaneously in one tissue section
- covalent signal deposition followed by elution of the anti-target antibody allows detection of the next target without fear of cross reactivity
- typical 4-plex protocols may be completed in less than 1 day, compatible with standard immunohistochemical methods
- quantitative results are possible when Opal is combined with Multispectral Imaging

Mark Dupal will describe Opal and the Vectra in detail and provide examples demonstrating their use in the early identification of progenitor cells, cancer immunology, assessment of microenvironment, co-localization of markers within specific sub-populations of cells and tracking cell signaling pathways.

28th August 2014 (Thursday)
0915-1045
Sabah Room

Symposium 12: Forensic neuropathology

Chairpersons: Jessie Hiu, Mohd Aznool Haidy Ahsorori

S12a. Traumatic neurological deaths

Ravindra Fernando

Department of Forensic Medicine, Faculty of Medicine, University of Colombo, Sri Lanka

Traumatic brain injury (TBI) caused by falls, vehicle accidents and violence, is a leading cause of death and disability around the globe and presents a major worldwide social, economic and health problem.

Traumatic neurological deaths (TND) as a result of TBI are a leading cause of mortality. TND can occur as a consequence of a focal impact upon the head, by a sudden acceleration/deceleration within the cranium or by a complex combination of both.

Types of brain injury that can cause TND include cerebral laceration, cerebral contusion, intracerebral haemorrhage, extradural haemorrhage, subdural haemorrhage, subarachnoid haemorrhage and intraventricular hemorrhage.

Deterioration and TND of some patients following primary brain injury (the damage that occurs at the moment of trauma when tissues and blood vessels are stretched, compressed, and torn) is caused by secondary injury. It is a complex set of cellular processes and biochemical cascades that occur in the minutes to days following the trauma, which include alterations in cerebral blood flow, cerebral hypoxia, cerebral oedema, raised intracranial pressure, damage to the blood–brain barrier, release of factors that cause inflammation, free radical overload, excessive release of the neurotransmitter glutamate, influx of calcium and sodium ions into neurons, and dysfunction of mitochondria. http://en.wikipedia.org/wiki/Traumatic_brain_injury - cite_note-Park08-55. Injured axons in the brain's white matter may separate from their cell bodies as a result of secondary injury, potentially killing those neurons.

Histologically, the loss of CA3 pyramidal cells in the hippocampus has been observed ipsilaterally in the cortical contusion and bilaterally in diffuse axonal injury. Injury-induced apoptosis can be detected from hours to days following injury and may contribute to neurological dysfunction. Early shock seems to be the major systemic secondary brain insult in patients with severe traumatic brain injury.

S12b. The role of postmortem CT scanning in the evaluation of traumatic head injury

[1]Mansharan Kaur Chainchel Singh, [2]Saiful Nizam Abdul Rashid

[1]Forensic Radiology Unit, Faculty of Medicine, Universiti Teknologi Mara, Shah Alam, [2]Radiology Department, Faculty Of Medicine & Health Sciences, UPM, Serdang, Selangor, Malaysia.

Traumatic head injuries are common and have a high morbidity and mortality. Until a few years ago, the demonstration of traumatic head injuries was mostly done during autopsy supplemented by radiography and histology. New diagnostic possibilities in forensic pathology have been provided with the introduction of computed tomography (CT) scanning. Due to its advanced 2D and 3D post-processing possibilities, CT in particular possessed certain advantages in comparison with autopsy with regard to forensic reconstruction. CT is better suited to the evaluation of osseous lesions, intracranial bleeds, intracranial tumours and pneumocranium. Concerning the cause of death, CT shows overall good correlation with autopsy. Despite the aforementioned, CT is to a varying extent inferior to autopsy in view of the detection of several craniocerebral findings. For example, due to technical limitations (limited resolution), lesions smaller than 3 mm regularly escaped the radiological analysis.

28th August 2014 (Thursday)
0915-1045
Selangor Room

Symposium 13: Cell based diagnosis & treatment

Chairpersons: Roshida Hassan, Eusni Rahayu Mohd Tohit

S13a. Detection of circulating solid tumour cells

Chee-Onn Leong

Center for Cancer and Stem Cell Research, Institute for Research, Development and Innovation (IRDI), International Medical University, Malaysia; School of Pharmacy, International Medical University, Malaysia

Circulating tumour cells (CTCs) were discovered nearly 150 years ago but their potentials have only been recognized recently as a feature of most solid tumours due to their extremely low concentration in the peripheral circulation. Several technologies have been developed to isolate and analyze CTCs, which can now be routinely accessed for clinical information. The most advance of these uses immunomagnetic selection of epithelial cell adhesion molecule to isolate CTCs for analysis. Studies using this system have demonstrated that categorization of patients into high and low CTC groups using a validated decision point is prognostic in patients with metastatic breast, colorectal, or prostate cancer. Attempts to use CTC counts to guide therapeutic decisions have yielded positive results and key concepts in clinical application of CTC information, including the CTC cutoff, predictive value in disease subtypes, and comparison to current evaluation methods, have been demonstrated. Clinical studies of the impact of CTC counts in routine clinical practice are ongoing. However, recent published evidence on the clinical use of CTCs in metastatic breast cancer continues to support these concepts, and experience in the community oncology setting also suggests that CTC enumeration can be useful for therapy management.

S13b. Disease modeling using induced pluripotent stem cell technology

Soon-Keng Cheong

Faculty of Medicine & Health Sciences, Universiti Tunku Abdul Rahman, Bandar Sungai Long, Kajang, Selangor, Malaysia

Yamanaka and colleagues reported the first successful establishment of induced pluripotent stem cells (iPSCs) lines in 2006. Further development and implications from this discovery render him the award of the Nobel Prize in 2012. While on-going research is directed largely to clinical translation of iPSCs for applications in regeneration medicine, an emerging area is their application in disease modelling to understand the underlying complex pathogenetic mechanisms of diseases. This came about when researchers realise that upon reprogramming somatic tissues of people to the pluripotent state and thus capable of generating tissues of all the three germ layers, the pathogenetic mechanisms of the diseased cells remain. The technology allows the creation of patient-specific and disease-specific cell lines for further investigation. It also provides an unlimited source of proliferating cells and overcomes the constraints of limited patient's sample, as well as limited proliferation capacity of diseased cells and loss of functionality observed in *ex vivo*-expanded cells. Previously, such study is undertaken on patient's samples or immortalised, tumour-derived cell lines. As iPSC lines can sidestep these limitations, they have now become an attractive human model for drug screening as well as basic research into the pathogenesis of diseases. In recent years, iPSC-disease models have been developed for this purpose.

To date, many have been established and continue to be established. The pioneering models reported so far include haemopietic, hepatic, endothelial, neurological and cardiovascular diseases. Collectively, these models have yielded findings that support the notion that iPSCs can reliably reproduce abnormal phenotypes and behaviours *in vitro* and thus provide crucial mechanistic insights into the disease process. In addition, the findings also suggest that iPSC technology may serve as a platform for functional study of small molecules such as drugs or biologicals. This could pave the way for potential patient-specific drug screening in a clinical setting as well as large scale pharmacological screening of drugs or biologicals in an industry-setting.

S13c. Can we use the immune system to conquer cancer?

Toh Han Chong

Department of Medical Oncology & Deputy Director, National Cancer Centre Singapore

The journal Science has voted Cancer Immunotherapy as the most important scientific breakthrough of 2013. Recent successful phase III clinical trials are testament to the relevance of the immune system in fighting human cancer.

In a phase II clinical study, we treated 21 patients with heavily pre-treated metastatic nasopharyngeal cancer (NPC) with non-myeloablative blood stem cell transplant (NST) using HLA-matched and 1-antigen mismatched sibling peripheral blood stem cell allografts. We demonstrate for the first time that NST can induce meaningful clinical responses in patients with advanced NPC with prolonged disease control achieved in some patients.

We also present a first-in-man clinical trial of an intradermal autologous dendritic cell (DC) cancer vaccine transduced with replication-deficient adenoviral vector Ad5f35 encoding truncated LMP1 and full-length LMP2 in 16 patients with pretreated metastatic NPC who have failed one or more lines of treatment and another lysate-pulsed DC vaccine trial in refractory colorectal cancer.

Autologous EBV-antigen specific cytotoxic T lymphocytes (CTL) can be activated, expanded and adoptively transferred as a cell-based immunotherapeutic strategy against virally-transformed cancers. We developed an adoptive cell therapy strategy of serial infusions of autologous EBV-specific CTL for first line treatment of advanced NPC patients following a course of potentially synergistic combination chemotherapy with gemcitabine + carboplatin. This Phase II study has completed accrual of all 38 patients with advanced NPC and interim clinical, biomarker correlates and translational results will be presented for discussion. With a median follow up of 2 years, median overall survival is 29.9 months and I year and 2 year survival are 77% and 63% respectively. These outcomes represent the most positive results of any systemic therapy against advanced NPC. I will provide an update of this mature, completed study and its translational aspects.

I will present an overview and update of the latest global cutting edge developments of immune based studies that have been proven to prolong survival in phase III clinical trials, including those that influence immune checkpoint processes such as anti-CTlA4Ig and anti-PD1 therapies, and provide an overall landscape of the latest in immunotherapy against cancer.

28th August 2014 (Thursday)
0915-1045
Kedah Room

Symposium 14: Sepsis/Emerging Infectious Diseases *(Chapter of Emergency Medicine, Academy of Medicine Singapore & College of Emergency Medicine, Malaysia)*

Chairpersons: Eillyne Seow, Shah Jahan

S14a. SARS to pandemic flu – A Singapore ED experience

Eillyne Seow

Ambulatory & Diagnostic Medicine, Tan Tock Seng Hospital, Singapore

We fought and won the war against SARS in 2003. It changed the way we looked at our world. Since 2003, we have realised that "bugs" do not recognise borders. The response to H1N1 in 2009 was swift.

In Singapore, during the SARS outbreak, one hospital was designated as 'SARS central'. It received only 'SARS patients'. This was the second largest hospital (Tan Tock Seng Hospital) with the busiest emergency department in the country. This containment strategy created a great strain on the health services. In 2009, this same hospital continued normal operations while receiving suspected H1N1 patients from the primary care physicians and the borders. Suspected H1N1 patients in the other hospitals were not transferred to Tan Tock Seng Hospital. This was a partial containment strategy.

People were the most important weapon that enabled us to win both wars. Leaders were cool, honest, clear, empathetic and inspirational. They engaged their teams and kept morale high. The presence of astute clinicians was important in the early detection and management of the two novel 'bugs'. Housekeeping and security colleagues were important members of the team.

Communication was critical in the containment of both infectious disease outbreaks. In Singapore the public was kept constantly informed through all forms of media. This helped to enlists public assistance and cooperation.

We learnt that infectious disease outbreaks are not alike after managing the 'SARS and H1N1 incidents'. It had been important to adapt, modify and adopt practices as the outbreaks and events unfolded.

Infectious disease outbreaks are unpredictable but the world today is better prepared than it has ever been.

S14b. Challenges in laboratory diagnosis during outbreaks of emerging infectious diseases in the developing world

Jamal I-Ching Sam

Department of Medical Microbiology, Faculty of Medicine, University Malaya.

Infectious diseases now spread easily and rapidly within the global community. To contain outbreaks, there first needs to be effective surveillance of disease, followed by diagnosis of the causative pathogen. Rapid diagnosis allows targeting of disease management, treatment, control and prevention measures, and is particularly critical in countries with limited resources. Real-time PCR is the main diagnostic method used for outbreaks of newly emerging or remerging pathogens, as it allows the rapid design of new assays, which give quick, sensitive and specific results. As new pathogens arise, such as MERS-coronavirus and H7N9 influenza in recent years, real-time PCR diagnostic protocols are quickly shared with everyone. However, even though this knowledge of acquiring new tests is now easily available,

developing countries still face many challenges in diagnosis of emerging pathogens, both during initial outbreaks and beyond, if these diseases become endemic. These challenges include lack of rapid, accurate and cheap assays, laboratory facilities, trained staff, funding, established national testing networks, and regulation of substandard tests. The 2009 H1N1 influenza pandemic and Chikungunya outbreaks will be used as illustrative examples.

S14c. Shock index as a prognostic marker of short term outcome in patients presenting with severe sepsis and septic shock

Shah Jahan Mohd Yussof[1], Mohd Idzwan Zakaria[2], Fatahul Laham Mohamed[3], Mohamad Adam Bujang[4]

[1]Hospital Kuala Lumpur, Kuala Lumpur, Malaysia, [2]University of Malaya, Kuala Lumpur, Malaysia, [3]Hospital Sultanah Bahiyah, Alor Setar, Malaysia, [4]Biostatistics Unit, Clinical Research Centre, Kuala Lumpur, Malaysia

Introduction: The importance of early recognition and treatment of sepsis and its effects on short-term survival outcome have long been recognized. Having reliable indicators and markers that would help prognosticate the survival of these patients is valuable and would subsequently assist in the course of effective dynamic triaging and goal directed management. This study is set to determine the prognosticative value of Shock Index (SI),taken upon arrival to the emergency department(SI-1) and after 2 hours(SI-2) of resuscitation on the short-term outcome of severe sepsis and septic shock patients. *Methodology:* This is a retrospective observational review involving 50 patients admitted to the University of Malaya Medical Centre between June 2009 and June 2010 who have been diagnosed with either severe sepsis or septic shock according to SIRS criteria.Diagnoses of severe sepsis and septic shock were determined from details recorded in the registration book of the resuscitation room. Shock Index on presentation to ED(SI-1) and after 2 hours of resuscitation in the ED(SI-2), age, gender, temperature, respiratory-rate, and blood pressure were taken.The data was analyzed with its median, minimum and maximum variables tested with Mann-Whitney U and Chi square analysis.ROC curves and AUC values were generated among these variables to assess prognostic utility for outcome. The outcome is defined as either death or survival to discharge. *Results:* Amongst all 7 variables tested, 2 were tested to be significant ($p:<0.05$). From the sensitivity, specificity and ROC analysis, the best predictor for death was SI-2 with a sensitivity of 80.77%, specificity of 79.17%, AUC value of 0.8894 [CI_{95} 0.8052, 0.9736] at a cut-off point of >1.0. *Conclusion:* SI-2 can be utilized as an effective and reliable predictor for death in patients presenting with septic shock and severe sepsis in an emergency department. The value of SI-1 is less sensitive and specific in predicting the same.

28th August 2014 (Thursday)
0915-1045
Perak Room

Symposium 15: National Ethics Seminar

Chairpersons: Baizurah, Veera Sekaran

S15a. POCT in haematology

Kuperan Ponnudurai

Dept of Haematology, Tan Tock Seng Hospital, Singapore

Point of Care Testing (POCT) is increasingly seen as a complimentary or alternate type of testing that meets specific care needs within a hospital itself in critical care settings or in ambulatory care settings like outpatient clinics, Physician laboratories, at Patients' home or in remote clinics in developing countries. The driving notion behind POCT is to shorten the Turnaround time which allows for immediate clinical management decisions. POCT available in Haematology include simple measurement of haemoglobin only, Complete Blood count with 3 or 5 part differential, measurement of International Normalised Ratio for anticoagulant monitoring and Thrombelastography/ Thrombelastometry in Critical Care settings. POCT is also available for rapid screening for Malaria and for CD4 Lymphocyte counting on patients with HIV out in the community with limited access to Central laboratory. Studies have shown that Thrombelastography/Thrombelastometry which is able to provide faster and more definitive information on the coagulation defect is becoming more popular for optimizing intra operative transfusion decision reducing the inappropriate use of blood products. POCT does not necessarily mean improved patient outcome unless the entire clinical pathway is optimized to achieve improved patient outcome.

A POCT Committee should be responsible for the clinical governance including assessment needs, training, risk assessment, quality control and finance. Management of POCT is challenging to assure Quality of testing and the devices should generate results that are comparable to those of the local laboratory and in order to achieve this, reliable internal Quality Control system and External Quality assessment Programme must be established and to enhance communication, immediate availability of POCT results within the Electronic Medical record.

S15b. Point of Care Testing in Clinical Chemistry: A General Overview

Sook-Fan Yap

Department of Preclinical Sciences, Faculty of Medicine & Health Sciences, Universiti Tunku Abdul Rahman, Bandar Sungai Long, Kajang, Selangor, Malaysia

Point-of-care tests (POCT) were developed out of a need for rapid test results for immediate patient management. In the hospital setting, this would be applicable in intensive care units, the emergency department and perhaps the operation theatre. A quick turnaround time for tests that can only be offered by POCT can also have a place in the primary care environment such as the general practitioner office and primary care clinics. In this latter situation, availability of results at the time of patient consultation provide for immediate feedback to patients on their state of health and informed clinical decision, as well as improve patient satisfaction and convenience.

POCT in the 1950's were largely manual tests, the most widely used being the urine dipstick test for urine chemistry and the urine pregnancy test, as well as the faecal occult blood test. Later development saw the introduction of simple devices for the automatic reading of urine test strip results, which removes the subjectivity in result reporting. Since then, there have been numerous developments in

POCT. These include improvement in device technology and advances in reagent manufacture which resulted in an ever increasing range of tests, decrease in testing time and increase in the simplicity of operation. Other developments are advances in procedures to control the analytical quality of the testing process, and electronic capture and management of test results.

In practical terms, current POCT require relatively small sample volume, and many employ whole blood samples. The devices are more potable, have built in lock out features, automatic calibration and automatic quality control. Some devices come with bar code scanning ability thereby simplifying patient and sample identification. However, connectivity of POCT devices to the laboratory information system remains a challenge. Nevertheless, some headway has been made in this area; in 2001, the "Connectivity Industry Consortium Document" was presented to CLSI leading to the formation of the consensus committee for POCT connectivity. Indeed, an increasing number of devices have started to use the POCT 1A standard which allows ease of integration across platforms.

However, despite the many development and advances, many issues regarding the POCT service remains. An important issue of concern is the organisation and management of the POCT service. The essentials of a POCT service are (1) support by a robust management structure and (2) integration with the laboratory service. The numerous guidelines published by the AACB provide a valuable resource for laboratory personnel involved in the POCT service. Some aspects covered by these guidelines include quality assurance, training, data management and continuous quality improvement.

Another key involvement of laboratory staff in the POCT service is the evaluation and selection tests and devices. The general principles in this regard should be no different from that for central laboratory test/equipment selection. However, it should be kept in mind that POCT are carried out by non-technical personnel at locations removed from the laboratory. Therefore, special considerations should be given to the technical as well as operational features of the tests and devices. An idealised wish list would include (1) minimally or non-invasive sampling, (2) accurate and reproducible test results (3) simple to use, intuitive and fool-proof devices, (4) reagent stability at room temperature, (5) desirable software features such as lockout, electronic system checks, etc. and (6) IT connectivity to allow ease of management by the central laboratory.

S15c. Ethical issues in point-of-care testing

Lai-Meng Looi

Department of Pathology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

The essence of the code of medical ethics is to do "good" and "not do harm." Because laboratory practice is an integral part of medical practice, the code applies equally to it, underscoring its responsibilities to patients, clinical colleagues and Society. Honesty, integrity and professionalism are principles of ethical conduct which pervade through all steps of laboratory practice, be they the collection of information, handling of samples, performance of tests, reporting of results, storage and retention of records, accessibility and confidentiality of records. Improper conduct at any step can lead to results that "do harm" more than "good." Because point-of-care testing (POCT) has the same ability to impact on care of patients as mainstream laboratory testing, the same ethical principles should apply. Yet while most laboratories have taken great pains to sure technical validity and competency in testing, such as through continual retraining of staff, practice of quality assurance and accreditation, the same cannot be said for POCT. POCT is notoriously difficult to control because of the diverse settings in which POCT is performed, and the large number and range of operators. The biggest challenges relate to ownership (and hence accountability) of POCT services, training and competency of operators, and the establishment of a quality management system. Additionally, conflict of interest issues arise when testing is not independent of the requester, with inherent impact on choice of equipment and services, and allocation of resources. The establishment of multidisciplinary POCT committees is the first step in the long path towards addressing the quality and ethical issues in POCT.

28th August 2014 (Thursday)
1115-1245
Sabah Room

Symposium 16: Diagnostic challenges in Cytology

Chairpersons: Sharifah Noor Akmal, Nurismah Md Isa

S16a. Challenges in thyroid cytopathology

Syed Z Ali

Johns Hopkins University School of Medicine and The Johns Hopkins Hospital in Baltimore, Maryland, USA

The pivotal role of FNA in the management of patients with thyroid nodule will be highlighted. The lecture will elaborate on diagnostic issues of practical importance and will describe the potential pitfalls leading to erroneous interpretation on FNA. Cytomorphologic characteristics of common thyroid nodules will be presented with reference to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Clinical implications of the various cytopathologic interpretations will be discussed as well as the management guidelines for each diagnostic category. The crucial role of a multidisciplinary approach will be emphasized throughout the presentation. Cytomorphologic features of various thyroid lesions prepared with liquid-based cytology will be shown and contrasted with those prepared with direct (conventional) smears. The lecture will also include a brief update on the use of new molecular markers used to enhance the pre-operative diagnostic accuracy of thyroid FNA.

S16b. Atypical squamous lesion – my approach

Gamze Mocan Kuzey

University of Near East, Lefkosa-TRNC, Mersin-10, Turkey

The conventional Pap smear has been mainstay of cervical cancer prevention for more than 70 years. By this success, it has been accepted as the most successful screening test. The success of Pap smear depends on the quality of obtaining and fixation of the sample, preparation, and cytologic examination. The success also depends on the performance of the cytopathologist, control of the positive and negative reports and ancillary techniques. Image analysers (rescreening), archives, consultation and use of common terminology in reporting (Bethesda System 2001) also play an important role. The spectrum of cervical cytologic abnormalities ranges from equivocal changes to the pathognomic nuclear and cytoplasmic effects of HPV infection to severe cytologic neoplastic changes. The terminology of the 2001 Bethesda System for the squamous epithelial cell abnormalities was accepted as;

Epithelial cell abnormalities
- Squamous cell
  - Atypical squamous cells (ASC)
    - of undetermined significance (ASC-US)
    - cannot exclude HSIL (ASC-H)
  - Low-grade squamous intraepithelial lesion (LSIL)
    - encompassing: human papillomavirus /mild displasia /cervical intraepithelial neoplasia (CIN)1
  - High-grade squamous intraepithelial lesion (HSIL)
    - encompassing: moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3
  - Squamous cell carcinoma (SQC)

My presentation will concern such cases with the differential diagnosis.

S16c. EUS FNA of pancreas

Syed Z Ali

Johns Hopkins University School of Medicine and The Johns Hopkins Hospital in Baltimore, Maryland, USA

Improved imaging techniques and the introduction of endoscopic ultrasound guidance has resulted in significantly better detection/recognition of pancreatic masses. Clinical and radiological examinations cannot reliably distinguish benign/inflammatory pancreatic disease from carcinoma, the latter being one of the most lethal human malignancy. Therefore, an accurate pre-operative diagnosis is crucial for optimal and timely patient management. The lecture will focus on diagnostic issues of practical importance and will describe the potential pitfalls and limitations leading to erroneous diagnosis on EUS-guided FNA of this difficult anatomic site. The importance of a multidisciplinary approach when dealing with pancreatic FNA will be highlighted as well as the clinical implications of cytologic interpretations. Emphasis will be placed on the role of ancillary studies particularly immunostaining in difficult to classify pancreatic tumors. Mimics of cancers such as chronic pancreatitis will be particularly discussed to avoid misdiagnoses. Morphologic challenges relating to cystic pancreatic lesions will also be presented. The presentation will also include a discussion on the new standardized terminology and nomenclature for pancreatobiliary cytology.

28th August 2014 (Thursday)
1115-1245
Selangor Room

Symposium 17: Molecular diagnostic testing in Haematology

Chairpersons: Zubaidah Zakaria, Soon-Keng Cheong

S17a. The molecular genetics of myeloproliferative neoplasms

Chieh-Lee Wong

Department of Medicine, UKM Medical Centre, Kuala Lumpur

The discoveries of JAK2 V617F and more recently CALR mutations have revolutionized our understanding of the molecular pathogenesis of myeloproliferative neoplasms (MPNs). However, to date, these mutations have not been shown to directly affect the clinical phenotypes and survival of patients with the various subtypes of BCR-ABL-negative MPNs.

Amongst the MPNs, the molecular pathogenesis of chronic myeloid leukemia is well established by the presence of BCR-ABL mutation. Constitutive tyrosine kinase activation appears to be a common pathogenetic mechanism. A number of protein kinases have been described in the BCR-ABL-negative MPNs. Janus kinase 2 (JAK2) gene is a member of Janus kinase family and is a central regulator of cytokine signaling pathways by virtue of its tyrosine phosphorylation activities. In 2005, the breakthrough discovery of somatic mutations in JAK2 gene has revealed that mutation of the JAK2 V617F gene causes substitution of phenylalanine for valine at position 617 in exon 14 of the JH2 pseudokinase domain of the JAK2 gene and can be found in majority of patients with polycythaemia vera and in more than 50% of patients with essential thrombocythaemia and primary myelofibrosis.

Although deregulation of JAK2 signaling plays a pivotal role in the pathogenesis of MPNs, it remains unclear why mutations in the JAK2 gene are associated with different MPN clinical phenotypes and JAK2 mutations are often secondary events. Over the recent years, other genes which are involved in the epigenetic control of gene expression (e.g.TET2, IDH1/2, ASXL1 and EZH2 mutations) have increasingly been identified. To date, these somatic mutations do not seem to be acquired in a particular order suggesting that the disease-initiating events remain to be identified. In addition, the finding of complex clonal hierarchies and chromosomal abnormalities in many cases suggests that genetic instability may play a role and may be inherited or acquired.

Further molecular studies are required to elucidate the genetic and epigenetic mechanisms behind the pathogenesis of this enigmatic stem cell disorder and to guide the treatment of patients in the era of rapidly evolving targeted therapies.

S17b. Epigenetic dysregulation and treatment in MDS

John Gibson

Institute of Haematology, Royal Prince Alfred Hospital, Sydney NSW Australia

MDS is a heterogeneous group of myeloid neoplasms characterised by a deeply variable clinical behaviour, which is a function of both disease-specific and individual patient characteristics. The later reflects age, PS and co-morbidities. Disease specific variation stems not only from aberrant karyotypes, but, as we now recognise, the additional complex interplay of epigenetic, immune regulatory and marrow microenvironmental alterations. The individual patent phenotype and response to therapy represents the sum of these variables.

Epigenetics refers to the establishment of heritable changes in gene expression without alteration in primary DNA sequences and plays an essential role in various biological processes. At least 3 major epigenetic mechanism are recognised; DNA methylation, histone modifications and nucleosome remodelling. Disruption of these processes is thought to lead to many human diseases including cancer.

In MDS, abnormal hypermethylation of promoter CpG islands in DNA is believed to lead to epigenetic silencing of key (tumour suppressor) genes, thus contributing to the development of this malignancy. DNA-methyltransferases (DMT) are responsible for the addition of CH3 to newly synthesised DNA (3A&3B) and maintenance of methylation (#1) in replicated DNA. The use of hypomethylating agents such as Azacytadine (AZA) and Decitabine (DAC) had led to a change in the natural history of some patients with higher risk MDS and their use is being evaluated in lower risk patients. For instance, compared to supportive care, AZA has been shown to prolong survival and delay leukaemic transformation whilst DAC can also induce responses and prolong progression free survival. Typical response rates include CR and PR in 20-30% and haematological improvement in 20-50% as well as "stable disease" and responses in therapy-related MDS.

Given the complexities and limitation of these agents, challenges for the future include not only the development of better agents but also predicting patient-specific responses.

S17c. Molecular diagnosis of von Willebrand Diseases (vWD)

Michael Laffan

Department of Haematology, Imperial College London, UK

In most cases the phenotypic analysis of VWF provides sufficient information to allow diagnostic classification and appropriate treatment. In this circumstance genetic analysis is superfluous. However there are a number of circumstances in which *VWF* analysis may either help clarify the specific disease type or may be helpful in explaining treatment response or predicting likelihood of inheritance.

1. The FVIII binding assay required for discrimination between mild or moderate haemophilia A and 2N VWD is technically difficult, time consuming and consequently performed only in a few centres. Genetic analysis of *VWF* exons 17-27 provides a rapid means of discrimination and should identify at least one missense VWF:FVIIIB mutation in patients with 2N VWD. Conversely, the diagnosis of haemophilia can be confirmed in the vast majority of cases by sequencing the *F8* gene.

2. Type 2B VWD and PT-VWD patients present with similar phenotypes. Again, the laboratory tests to discriminate between the two are difficult and genetic analysis provides a ready and attractive alternative. Mutations causing type 2B have been identified in exon 28 of *VWF* and PT-VWD mutations lie in *GP1BA* exon 2. Clearly the distinction is important for appropriate therapy.

3. Prenatal diagnosis is probably appropriate only in families with type 3 VWD: usually when the parents already have one affected child. If at least one mutation in the affected child can be identified then antenatal diagnosis is possible.

4. Sometimes difficult cases with unexpected results or desmopressin response may be illuminated by genetic analysis which can explain features such as accelerated clearance.

5. When a diagnosis of VWD is made it is appropriate to test first degree relatives with or without a positive bleeding history. In some circumstances this may be clarified by family testing.

28th August 2014 (Thursday)
1115-1245
Kedah Room

Symposium 18: Oncology

Chairpersons: Sunil Sethi, Muhammad Arif M Hashim

S18a. Circulating tumour cells (CTC) as biomarkers in personalised oncology

Tar-Choon Aw

Singapore Institute of Advanced Medicine, Singapore

Cancer patients are monitored for recurrence using clinical findings, biomarkers, and imaging; CTC detection is a new modality. While many methods for CTC analysis exist, the CellSearch CTC assay is the first and only FDA-approved assay. CTCs are captured by antibodies directed against epithelial cell adhesion molecules. The captured cells are then labelled with fluorescent antibodies against intracellular cytokeratins (8,18,19), nucleus (DAPI), and leukocytes (CD-45). Following immuno-fluorescence microscopy fluorescent objects (DAPI +ve, cytokeratin +ve, and CD-45 –ve) are counted as CTCs. CTCS are not found in normal subjects and benign conditions.

CTCs offer useful information for monitoring disease progression and treatment response. In a recent meta-analysis, presence of CTCs was associated with an increased risk of breast cancer (BC) progression (n=4978). Furthermore, CTCs were also associated with an increased risk of mortality (n=5832). CTCs were associated with both progression-free (PFS) and overall survival (OS) in early stage BC (19 studies) and in metastatic disease (12 studies). CTCs detected before, during, and after systemic therapy showed similar prognostic value for both endpoints. In patients with presumed non-metastatic BC (M0), presence of CTCs renders them in a higher stage M0(i+).

In prostate cancer patients with hormone-resistant tumors (n=231) the number of CTCs predicted disease progression and OS. Median PFS was significantly longer for the favorable group compared to the unfavorable group (5.8 versus 4.2 months) as was the median OS (21.7 versus 11.5 months). In metastatic colorectal cancer (n=430) CTCs also predicted disease progression and OS. Median PFS was significantly longer for the favorable group compared to the unfavorable group (7.9 versus 4.5 months) as was the median OS (18.5 versus 9.4 months).

CTCs are increasingly important in the management of patients with breast, prostate and colon cancers and possibly in other cancers (lung, gastrointestinal, genitourinary, gynaecologic, and head & neck).

S18b. Pharmacogenomics of docetaxel for breast cancer

Johnson Stanslas

Pharmacotherapeutics Unit, Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia

Docetaxel is an antitubulin chemotherapeutic agent approved for the treatment of breast, lung, ovarian and non-hormonal dependent prostate cancers. However, the success of this drug is limited by adverse events (AEs), the severity of which ranges from tolerable to life threatening. Tapering the dose or changing the regimen would limit the use of docetaxel. Therefore, the present study was conducted involving 110 Malaysian breast cancer patients of different ethnic groups (Malays, Chinese and Indians) to investigate the association between docetaxel AEs and single nucleotide polymorphisms (SNPs) of genes encoding for proteins involved in the metabolism and transport of docetaxel. Eligible consented

patients enrolled in the study were recruited from University Malaya Medical Centre (UMMC) and Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The ethnicity of breast cancer patients in this study consisted of 40% Malays (n=44), 52% Chinese (n=57) and 8% Indians (n=9). Fatigue (50%), nausea (35%) and mucositis (31%) were the most commonly reported non-hematologic AEs. The SNPs of enzyme cytochrome P450 3A5 (*CYP3A5* 6986A>G), and transporters ATP-binding cassette (*ABCB1* 3435C>T, *ABCB1* 2677G>T/A and *ABCC2* 1249G>A) as well as solute carrier organic anion transporter (*SLCO1B3* 334T>G) had significant influence on the development of docetaxel AEs. Rash was significantly associated with *ABCB1* 3435CT polymorphism: 36% of Chinese patients who were carriers of heterozygous genotype developed rash, while it only occurred in 21% of Malay carriers. It is worth noting that the Indians did not develop rash although 44% of them had heterozygous genotype. As such, it can be said that Chinese who are carriers of the heterozygous genotype are at high risk of developing rash. Moreover, since the heterozygous and mutant genotypes showed higher prevalence than the wild type, the rash is very likely related to mutant allele (T). Interestingly, the wild type GG of *ABCB1* 2677GA was associated with fatigue in 60% of Malays, 53% of Chinese and 33% of Indians. However, the difference among the ethnic groups was not statistically significant. Mucositis was associated with the coexistence of *CYP3A5* 6986AA (wild type) and *ABCB1* 3435TT (mutant). This preliminary study indicates SNPs-AEs associations could be used to individualise treatment to reduce AEs of docetaxel in Malaysian breast cancer patients.

S18c. Tumour markers

Leslie C Lai

Gleneagles Kuala Lumpur, Kuala Lumpur, Malaysia

Tumour markers are substances related to the presence or progress of a tumour and may be present in higher than normal concentrations in tissue and body fluids of cancer patients. Serum tumour markers may be used to aid cancer diagnosis and help determine prognosis, guide and monitor response to treatment, detect recurrence and be used as screening tests. When tumour markers are requested and interpreted correctly they contribute significantly to clinical management. Inappropriately used tumour marker results can cause patients anxiety and distress and lead to unnecessary investigations that may be associated with significant side-effects and potentially delay the correct diagnosis and treatment, in addition to increasing healthcare costs. Based on the National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines on Tumour Markers, αFetoprotein (AFP) may be used in conjunction with abdominal ultrasound for early detection of hepatocellular carcinoma (HCC) in patients with chronic hepatitis or cirrhosis due to hepatitis B or C infection. After a diagnosis of HCC, post-treatment monitoring with AFP is recommended as an adjunct to imaging. For testicular cancer, AFP, human chorionic gonadotropin, and lactate dehydrogenase are recommended for diagnosis, staging, prognosis determination, recurrence detection, and therapy monitoring. Prostate-specific antigen (PSA) is not recommended for prostate cancer screening, but may be used for detecting disease recurrence and monitoring therapy. Free PSA is useful in differentiating malignant from benign prostatic disease when total PSA is <10 µg/L. In colorectal cancer, carcinoembryonic antigen is recommended for prognosis determination, post-operative surveillance, and therapy monitoring in advanced disease. CA125 is recommended with transvaginal ultrasound for early detection of ovarian cancer in women at high risk for this disease. CA125 is also recommended for differential diagnosis of suspicious pelvic masses in postmenopausal women, as well as for detection of recurrence, monitoring therapy, and prognosis determination in women with ovarian cancer.

28th August 2014 (Thursday)
1115-1245
Perak Room

Symposium 19: Emerging Paradigm of Genomic- and Proteomic-Based Microbiology

Chairpersons: Zubaidah Abdul Wahab, Zetti Zainol Rashid

S19a. From genome to vaccine via the proteome

Sheila Nathan

School of Biosciences and Biotechnology, Faculty of Science & Technology, Universiti Kebangsaan Malaysia, Selangor, Malaysia

Since the first introduction of the smallpox vaccine by Edward Jenner, the field of vaccinology has made leaps and bounds in the development of vaccines against agents of infectious diseases. With the introduction of 'omics-based technologies, strategies to develop new vaccines have moved away from the more conventional "isolate–inactivate–inject" paradigm of utilising attenuated microbes or inactivated bacterial products. Instead, strategies such as reverse vaccinology and vaccinomics have taken advantage of the availability of microbial genome sequences, secretome data and systems biology. Reverse vaccinology uses the entire protein repertoire of each pathogen to select the best candidate vaccine antigens. More specifically, transcriptomics and proteomics enable the exploration of the range of antigens actually expressed by a pathogen under specified conditions, by examining the transcripts and proteins of the organism of interest, respectively. The 'omics-derived information can also provide additional information on proteins that are surface exposed (surface proteome) or genes that are functionally important for infection (functional genomics), antigens that interact with the host immune system and mechanisms involved in these interactions (immunomics), structural epitopes of immunogenic antigens (structural vaccinology) and, most recently, how individual host immune systems respond to a vaccine (vaccinomics). This has allowed the development of vaccines that were previously difficult or impossible to make with more promise in future discovery of unique antigens that may improve existing vaccines. This talk will elaborate on selected strategies with corresponding examples illustrated.

S19b. Applications in clinical microbiology

Zamberi Sekawi

Universiti Putra Malaysia, Serdang, Malaysia

Clinical microbiology which is a branch of pathology, has always been seen as 'outdated' when compared to the other disciplines in pathology. The techniques used for culturing bacterial pathogens dated back in the 19th century and it is still relevant to-date, serving their purpose well for patient care. With the advancement of molecular technology particularly genomic- and proteomic-based, clinical microbiology is about to undergo a paradigm shift in how it can support patient care through laboratory services. The current challenge is how to integrate this state-of-the-art technology into daily practice of clinical microbiology. In order for it to be accepted into clinical use, it has to be able to enhance clinical microbiology workflow, decrease patient length of stay, and reduce hospital costs. Whole-genome sequencing of bacteria has recently emerged as a cost-effective and convenient approach for addressing many microbiological questions. It can be used to identify the species of an isolate, test its properties, such as resistance to antibiotics and virulence, and monitor the emergence and spread of bacterial pathogens. It has to be sufficiently fast, accurate and cheap to be used in routine clinical

microbiology practice, where it could replace many complex current techniques with a single, more efficient workflow. Applications for proteomics are relevant to all of biology and provide a means to utilise genomic data in a more effective way. In taxonomy, it is possible that proteome profiling can be used as both a rapid characterisation tool as well as an identification tool. Within the predicted proteome, antigens may be selected for serological applications and the development of monoclonal antibodies and vaccines. With the recent development, both genomic- and proteomic-based technologies will provide an exciting paradigm shift day-to-day clinical microbiology practice.

S19c. Detection of antibiotic resistance

Norazah Ahmad

Bacteriology Unit, Institute of Medical Research, Ministry of Health Malaysia

The determination of the antimicrobial susceptibility of a clinical isolate for optimal therapy of infected patients is crucial especially when there is increasing resistance and emergence of multidrug-resistant microorganisms. The resistance to antibiotics can be caused by a variety of mechanisms which include the presence of an enzyme that inactivates the antimicrobial agent, a mutation in the antimicrobial agent's target, reduced uptake of the antimicrobial agent, active efflux of the antimicrobial agent; and overproduction of the target of the antimicrobial agent. Antibiotic resistance phenotype is usually detected using growth inhibition assays performed in broth or by agar disc diffusion. This involves disk diffusion methodology or Etest. Automation such as VITEK2™, Phoenix, Microscan and WalkAway has alleviated the laborious manual MIC determination. Molecular detection techniques for resistance such as quantitative PCR or microarrays are able to determine the presence of specific resistance genes and these have improved diagnosis by providing results within hours. MALDI-TOF MS has been applied to detect antibiotic resistance by detecting the biological activity of enzymes responsible for modification of antibiotic molecules. Newer generation sequencing procedures has allowed for full sequencing of entire bacterial genomes and is applicable in the context of antimicrobial resistance. Characterization of antibiotic resistance determinants at the genomic level plays a critical role in understanding, and potentially controlling, the spread of multidrug-resistant (MDR) pathogen. Following rapid advances in whole genome sequencing, proteomic technologies have been widely used to investigate microbial gene expression and the contribution of proteomics in identifying microbial drug resistance mechanisms.

28th August 2014 (Thursday)
1445-1615
Sabah Room

Symposium 20: Gastrointestinal pathology

Chairpersons: Hairuszah Ithnin, Effat Omar

S20a. Molecular basis, differential diagnosis and risk stratification of GIST

Chin-Yuan Tzen

Department of Pathology and Lab Medicine, Cathay General Hospital, Taipei, Taiwan

GIST is derived from progenitor cells of the gastrointestinal tract, which normally undergo differentiation into pacemaker cells or smooth muscle cells. KIT or PDGFRA mutation dictates the differentiation pathway leading to pacemaker cell. Tumors associated with KIT or PDGFRA mutation are categorized as mutant GISTs. In contrast, the wild-type GISTs are free of KIT or PDGFRA mutations, but are sometimes associated with BRAF or SDH mutations. The typical morphology of GIST is not much different from smooth muscle tumor and other mimickers. Therefore, differential diagnosis relies on mutational analysis (KIT and PDGFRA), FISH (MDM2) and immunohistochemical panel (CD117, DOG-1, desmin, ALK, and LSD-1). Once diagnosis is made, GISTs should be stratified according to their malignant potential. Based on tumor size, mitotic index, and tumor location, GISTs can be further divided into low-, intermediate, and high-risk groups, each of which is associated with a distinct risk of disease progression. Therefore, risk stratification provides a rationale for individualized treatment.

S20b. Application of molecular techniques in gastrointestinal pathology

Manuel Salto-Tellez

School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland, UK

Lecture adapted from: *Salto-Tellez et al, Chapter 15 – Tumours of the Gastrointestinal System; in 'Molecular Pathology: A Practical Guide for the Surgical Pathologist and Cytopathologist' Bartlett, Shaaban and Schmitt editors, to be published this year.*
Of all the organ systems, the gastrointestinal (GI) tract is, together with breast and lung, a main target for molecular diagnostics. Within the GI tract, most of the interest in molecular diagnostics to date has been focused on colorectal cancer (CRC), with the notable exceptions of *HER2* amplification testing in gastric cancer and *KIT/PDGFRA* mutational testing in gastrointestinal stromal tumour (GIST).

Despite extensive knowledge of the molecular biology of CRC, a comprehensive molecular therapeutic classification of the disease is lacking. The well-known adenoma-carcinoma sequence by Vogelstein and colleagues has been subsequently complemented by the Epidermal Growth Factor Receptor (EGFR) pathway, the chromosomal instability pathway (the one more closely associated with Vogelstein's original morpho-molecular sequence), the APC-αcatenin-Wnt signalling pathway, the microsatellite instability pathway and the description of the "methylator" genotype. Unfortunately, these categories are far from exclusive and overlap in a significant manner. In parallel with this unresolved taxonomical issue, there are single biomarkers in CRC that are tested routinely in molecular diagnostic laboratories to make key diagnoses, as well as more complex genetic signatures that allow prognostication; both will be presented here. Gastrointestinal stromal tumours and gastric adenocarcinomas are the other two main cancer types having specific tests with a clear therapeutic value. Regardless of the cancer type, we have divided these tests in two main groups, namely those with a primary diagnostic/genetic value, and those tests with a predominantly therapeutic value. Test

with a Predominant Diagnostic Value: *APC* Mutation Detection; MMR IHC; MSI Analysis; *MYH* mutation detection. Test with a Predominant Therapeutic Value: *RAS* mutation detection; *BRAF* mutation detection; Thymidylate synthase expression; MSI Analysis; *PIK3CA* mutation detection; Gene Expression Signatures; *HER2* amplification; and *KIT* and *PDGFRA* mutation detection.

This lecture will review all these tests, as well as the new, incipient taxonomy of CRC based on high-throughput genomic analyses.

S20c. Molecular basis and clinical implications of NET

Chin-Yuan Tzen

Department of Pathology and Lab Medicine, Cathay General Hospital, Taipei, Taiwan

Recent studies on the genetic and epigenetic aberrations cast a new light on the tumorigenesis of neuroendocrine neoplasms. The most common defect is that of chromosome assembly as MEN1, DAXX, ATRX mutations occur in 44%, 25% and 18%, respectively. These mutations cause epigenetic abnormalities and affect the expression of the proliferative regulator molecules such as p18, p27, and cyclin. As the epigenetic abnormalities indirectly affects cell proliferation, MEN1, DAXX, ATRX play a weak driver mutation in the development of NET. This concept correlates with the fact that tumors without typical epigenetic alterations are associated with worse prognosis. Mutations in NETs also occur in TSC2, PTEN, and PIK3CA. Tumors of this group are associated with worse prognosis. Taken together, molecular profile provides prognostic implication and has a potential to serve as a supplement of tumor grading. It appears that deciphering the molecular basis of neuroendocrine neoplasms provides us clinical implication.

28th August 2014 (Thursday)
1445-1615
Selangor Room

Symposium 21: Holistic forensic pathology – from macroscopy to molecular level

Chairpersons: Mohd Shah Mahmood, Mohd Azaini Ibrahim

S21a. Christchurch earthquake DVI operation

Simon Stables

National Forensic Pathology Service, Auckland, New Zealand

On 21st February 2011 a 6.3 magnitude earthquake hit the city Christchurch in the South Island of New Zealand resulting in the loss of 181 lives. This was the second largest natural disaster to have occurred in NZ. While the possibility of a large scale disaster had always been considered prior DVI planning had been limited.

Over the following 2 days a temporary mortuary was built in a LAV hanger at the Burnham military camp, approximately 30 mins from the Christchurch CBD. Limited autopsies were performed to determine cause of death in addition to recording identifying characteristics. The first autopsy was performed on 24th Feb with all autopsies being completed by March 7th. DVI assistance was received from multiple countries.

177 individuals from 22 countries were formally identified by the dvi process. Fingerprints and odontology were the main identifiers. Forty four bags of human remains were interred at a memorial site.

Despite the relative success of this operation in terms of the time taken for identification and the percentage of individuals identified there were significant issues with respect to communication, control, body preservation, and public and political expectations.

The coronial inquest later examined the survival potential of selected deceased and the adequacy, organisation and scene management of the fire service and urban search and rescue response. The evidence of the forensic pathologist was vital in assisting the coroner in this matter.

S21b. Practice of forensic histopathology: Malaysian perspective

Mohd Suhani Mohd Noor

Department of Forensic Medicine and Forensic Medicine Specialist, Hospital Sultanah Bahiyah, Alor Setar, Kedah

Forensic histopathology is a specialised field in pathology practice and may be deemed indispensable for ensuring good forensic pathology practice. Nevertheless it may be overshadowed by its more conspicuous clinical histopathology counterpart when it comes to the allotment of limited available resources. This is especially so when the forensic pathology service is provided by public hospitals in tandem with clinical patient care, as opposed to the service being provided by a medicolegal institute or a public health agency that is not directly engaged in patient care. In Malaysia forensic histopathology is still a nascent field; a reflection of erstwhile misapprehension that the microscopic tissue examination in forensic pathology practice can be handled the same way as in surgical pathology practice, without understanding the differences in scope and emphasis of histology between the two practices. The practice of forensic histopathology will be presented in the context of the forensic pathology services provided by public hospitals in Malaysia where death investigation is primarily selective rather than comprehensive, the main emphasis being in the detection of criminal and other

unnatural or unexpected deaths. The challenges in developing the practice of forensic histopathology in Malaysia will be discussed. Among the issues that will need to be addressed before the full potential of forensic histopathology can be realised in forensic pathology practice in Malaysia include improved postgraduate training in forensic histopathology and longer basic exposure to surgical histopathology, better access to histopathology laboratories for forensic pathology practice and the need to develop the subspecialised fields of forensic paediatric pathology and forensic neuropathology.

S21c. Autopsy pathology of New Zealand's TRAGADY initiative

Simon Stables

National Forensic Pathology Service, Auckland, New Zealand

The Investigation of Sudden Cardiac Death In New Zealand

Prior to the early 2000's the cause of death of young persons, for which no cause was found following a comprehensive autopsy, would be designated as *Unascertained* or some other similar unhelpful term or phrase. This was a less than satisfactory conclusion for the pathologist and coroner, and most importantly for the family.

In NZ a small group of interested cardiologists decided that more could be done to investigate these cases and set up the cardiac inherited disease registry and Cardiac Inherited Disease Group (CIDG). Initially all cases of SIDS / SUDI were referred to the group. Cardiologists attempted to follow up all families and blood samples were sent to overseas for channelopathy testing. Difficulty in contacting families and a very low yield from the genetic testing saw modification of requirement for genetic testing in this type of death. Instead DNA is now stored and referral for testing is made if clinically indicated.

In other sudden deaths (epileptics, drowning, sudden unexplained deaths, cardiomyopathies) blood is also routinely collected and the DNA stored, only being tested if clinically indicated.

In those deaths where there was a strong suspicion of an arrhythmic death, the case is referred to the CIDG who review the case and arrange to meet with and examine the family. Simultaneously the genetic testing is also performed. If required, the family is then followed by the cardiology dept.

Over time this has developed into a national group known as Cardiac Inherited Disease Group (CIDG) which includes cardiologists, pathologists, clinical and molecular geneticists, molecular biologists, paediatricians, genetic counsellors and support personnel. CIDG is also a member of the Australasian TRAGADY group.

28th August 2014 (Thursday)
1445-1615
Kedah Room

Symposium 22: Metabolic Medicine

Chairpersons: Roberto Verna, Leslie Charles Lai

S22a. Vitamin D in metabolic disease

Morris HA

School of Pharmacy and Medical Sciences, University of South Australia, and Chemical Pathology, SA Pathology, Adelaide, South Australia

The well characterised endocrine pathway of vitamin D metabolism and its activities are solely responsible for vitamin D regulation of plasma calcium and phosphate homeostasis under control of serum 1,25-dihydroxyvitamin D, the biologically active metabolite of vitamin D. This pathway protects against the metabolic bone disease of osteomalacia in adults or rickets in children. The critical level for serum 25-hydroxyvitamin D to maintain adequate serum 1,25-dihydroxyvitamin D is 20 nmol/L (8 ng/ml). In contrast a large body of data demonstrates that an adequate vitamin D status protects against osteoporosis, improving bone mineral density and reducing the risk of fracture. This evidence extends to the relationship between serum 25-hydroxyvitamin D and bone mineral density and reduction of fracture risk. Serum levels of 1,25-dihydroxyvitamin D do not relate to osteoporosis nor does administration of 1,25-dihydroxyvitamin D reduce the risk of fracture. Bone cells metabolise 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D to elicit biological responses including osteoblast maturation, reducing bone resorption, and enhancing mineral retention in bone. Such actions protect against bone loss and reduce the risk of fracture in the elderly. The critical level for serum 25-hydroxyvitamin D for optimising the health of the skeleton is approximately 75 nmol/L (30 ng/ml). This example from calcium and bone mineral homeostasis of two critical levels for serum 25-hydroxyvitamin D to protect against either osteomalacia or osteoporosis arises from the synthesis of 1,25-dihydroxyvitamin D in different organs, the kidney and skeleton respectively. These organs have different capacities to induce expression of the enzyme 25-hydroxyvitamin D-1-hydroxylase (CYP27B1) to different levels.

22b. Laboratory diagnosis and monitoring of diabetes and related metabolic syndromes

Sunil Sethi

Department of Laboratory Medicine, National University Health System, Singapore

Multiple laboratory tests are used to diagnose and manage patients with diabetes mellitus. In addition to long-standing criteria based on measurement of plasma glucose, diabetes can be diagnosed by demonstrating increased blood hemoglobin A1c (HbA1c) concentrations. Monitoring of glycemic control is performed by self-monitoring of plasma or blood glucose with meters and by laboratory analysis of HbA1c. “The metabolic syndrome” is the name for a clustering of risk factors for cardiovascular disease and type 2 diabetes that are of metabolic origin. These risk factors consist of atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, a pro-thrombotic state, and a pro-inflammatory state. The metabolic syndrome is often associated with a 2-fold increase in the risk of cardiovascular disease and a 5-fold increase in the risk of type 2 diabetes. A clinical diagnosis of the metabolic syndrome is useful because it affects therapeutic strategy in patients at higher risk, and focuses the clinical care to be complete with therapeutic targets for glycemic, lipid, blood pressure control. Laboratory testing plays a vital role for successful diagnosis and long-term monitoring of diabetes mellitus and related metabolic disorders.

S22c. High-density lipoprotein confer protection against atherosclerosis: the facts and the myths

Hapizah Mohd Nawawi

Faculty of Medicine, Universiti Teknologi MARA

There is unequivocal evidence, including those from epidemiological studies, that plasma high-density lipoprotein cholesterol (HDL-c) concentrations have inverse relationship with the risk of atherosclerotic cardiovascular disease (CVD). Hence, it has been assumed that this reflects the protective functions of HDL, which include their ability to promote cholesterol efflux, leading to the hypothesis that HDL confer atheroprotection. *In vitro* studies reported that HDL has numerous anti-atherogenic properties but there is still lack of validation of these functions in humans. Several animal studies and clinical trials support an atheroprotective role of HDL, albeit most of these findings were obtained in context of marked changes in other plasma lipids. The evidence from most preclinical and some clinical studies show that HDL promotes atherosclerotic plaque regression, from a combination of reduced plaque lipid and macrophage contents, as well as from a reduction in its inflammatory state, when the concentrations of functional particles are increased from either endogenous or exogenous sources. Finally, genetic studies in humans have not provided convincing evidence that HDL genes modulate cardiovascular risk. Furthermore, several recent pharmacological and genetic studies have failed to demonstrate that increased plasma HDL-C concentrations resulted in decreased CVD risk, giving rise to a controversy regarding whether plasma concentrations of HDL-C reflect HDL function, or that HDL is even as protective as assumed. Although more research will be needed regarding basic mechanisms and establishing how these changes translate clinically to reduced cardiovascular disease events, the findings that HDL can regress plaques suggests that the recent trial failures do not eliminate HDL from being a potential atheroprotective agent but rather emphasises the important distinction between HDL function and plasma concentrations. Therefore, despite overwhelming information on this intriguing lipoprotein, future research is essential to prove that the HDL hypothesis is correct.

28th August 2014 (Thursday)
1445-1615
Perak Room

Symposium 23: Issues in Microbiology & Infectious Diseases

Chairpersons: Ariza Adnan, Aniz Suriani Mohd Ali

S23a. Antifungal therapeutic drug monitoring; has it come of age?

Deborah Marriott

St. Vincent's Hospital, Sydney, Australia

Fungal infections are an important cause of morbidity and mortality in immuno-compromised patients. The associated high mortality rate has resulted in increasingly widespread use of antifungal prophylaxis with azole drugs (voriconazole, posaconazole, itraconazole and fluconazole) the most commonly administered agents. Therapeutic drug monitoring (TDM) is rarely systematically performed for these drugs; however, more broadly, there is increasing recognition, of the important role of TDM for azole antifungal agents when used for both prophylaxis and treatment.

There is a growing body of evidence highlighting the importance of azole TDM for both efficacy and toxicity in the hematology/bone marrow transplantation setting. However, data in the solid organ transplantation setting and for other immuno-compromised patients is extremely limited, making extrapolation from other patient groups necessary. It is now well recognized in haematology patients that adequate trough levels of posaconazole, itraconazole and voriconazole are required for efficacy, and that high plasma/serum levels may be associated with toxicity, particularly in case of voriconazole. However to date there has been only a single randomized study to confirm the impact of voriconazole TDM on patient outcome.

In complex patients such as transplant recipients receiving poly-pharmacy with interacting immuno-suppressive and other agents, and with underlying conditions that alter drug distribution and metabolism such as cystic fibrosis, therapeutic drug monitoring is strongly recommended to optimize efficacy and minimize toxicity. However the variability in absorption, metabolism and excretion of the azole agents in all patient populations is such that TDM should be considered part of routine clinical care.

S23b. Areas for improvement in microbiology services: A clinician's perspective

Suresh Kumar

Department of Medicine, Hospital Sungai Buluh, Malaysia

Management of infectious diseases is changing in many ways. Increasing resistance and its resultant more wide spread use of broad spectrum agents as the initial empirical therapy has resulted in dearth of effective antibiotics. With the lack of new antibiotics, there has been a steady decline in the acceptable safety bar for the antimicrobials, especially in the hospital settings.

Given this setting, there is increased emphasis on precise diagnosis, and early refinement of antibiotic therapy. So, the labs have a pushed into a new role of helping antimicrobial stewardship. Over-treatment for the majority, in order to prevent under-treatment in a few is common practice. To prevent this, we need better biomarkers that can quickly identify patients with bacterial infection. In addition we need rapid identification of resistant pathogens, so that early refinement of antimicrobial treatment can happen.

S23c. Quality improvement in infection control: challenges in an NICU

Nem-Yun Boo

Department of Population Medicine, Universiti Tunku Abdul Rahman

Nosocomial sepsis is a common problem in many neonatal intensive units. A number of evidence-based infection control measures have been identified over the years. These include good hand hygiene practice, sterile techniques in performing invasive procedures, proper hub care, good bundle care in handling total parenteral nutrition (TPN), and minimal duration of TPN, and judicious use of antibiotics. However, nosocomial sepsis continue to be high in many NICUs worldwide.

The main challenges for NICUs to achieve and sustain low nosocomial infection rates include: continuing support from the hospital administrators and hospital infection control unit, and leaders of medical and nursing staff; maintenance of an effective infection control team; timely education, monitoring and re-education of new staff on sepsis control; adoption of evidence-based policy to ensure good hand hygiene, judicious antibiotic usage, long line insertion and TPN administration; adoption of a simple yet effective monitoring system; and identification of a effective method to ensure rapid buy-in by both medical and nursing staff on the importance of good hand hygiene.

In recent years, the rapid cycle quality improvement (QI) method using the Plan, Do, Study, and Act (PDSA) format to identify effective changes has been reported to help NICU to improve nosocomial infection control. Using this method to improve the clinical, operational and organization systems of the NICU, coupled with regular monitoring of compliance of processes and outcome, effective team work, timely feedback to staff, and timely education of all new staff, a local NICU adopting these practices has witnessed a consistent and progressive reduction in nosocomial sepsis over the past four year.

26th August 2014 (Tuesday)
1130-1330
Sarawak Room

Lunch Symposium 1

LS1a. Roche
Moderator : Nurismah Md Isa

Innovations in digital pathology

Josh Jordan

High resolution imaging is changing pathology in profound ways. The ability to view any slide, anywhere, anytime is improving patient care by enabling access to consults and second opinions that simply aren't possible with glass slides. Many labs envision fully digital workflow for pathologists, with software designed to ease workload, improve collaboration, and provide decision support for difficult cases through image analysis. This presentation will review the current state of digital pathology hardware and software, discuss common challenges and pitfalls in adopting the technology, and provide real world examples of how the technology is being used in Asia to improve patient care and enable pathologists.

LS1b. Abbott Diagnostics
Moderator: Hanita Othman

Driving transformation change in the laboratory: Comparison of a centralized and a non-centralized laboratory system at a 1,500- bed University Hospital in Thailand.

Pimpun Kitpoka

Objective: To study whether the ACCELERATOR Automatic Processing System (APS) can improve laboratory operational efficiencies in terms of Turn Around Time (TAT) accomplishment, reduced process steps, less personnel and consumables usage reduction in a university hospital laboratory. *Relevance:* The ACCELERATOR APS is an innovative system that has ability to consolidate pre-analytic, analytic and post-analytic processes together in one platform. *Methodology:* One week data of TAT achievement percentage and consumables usage of 42 chemistry and immunology tests, as well as the waiting time from phlebotomy room, were obtained from laboratory information system; whereas, the working steps, and personnel requirements were obtained by workflow observation. Data and information from a new laboratory designed using centralization concept and having the ACCELERATOR APS installed were compared with those from the old laboratory, in which tests were separated into multiple analytical sections. *Validation***:** TAT was measured from the time patients registered at the phlebotomy room until their results were released, consumables usage and waiting time from phlebotomy was analyzed using LIS data. Working steps and personnel requirement came from workflow observations inside the laboratory. *Results:*

Metrics	Old Laboratory (Non-centralized)	New Laboratory (APS implemented)	% change
Tested samples	46,728	54,993	17.7%
% Achieved TAT goal	90.5%	96%	10.6%
Working steps	30	9	-70.0%
Personnel	12	4	-66.7%
Drawing sample tube usage	6,418	6,313	-1.6%
Barcode usage	6,418	6,313	-1.6%
Aliquot tip usage	5,548	0	-5,548%
2nd cup for aliquot usage	5.548	0	-5,548%
Average waiting time in phlebotomy room (mins)	15	4	-73.3%

Conclusion: Implementation of the ACCELERATOR APS was able to make the Hospital Laboratory more efficient. By adopting LEAN principles, the laboratory reduced wasteful and unnecessary steps by combining pre-analytical, analytical and post-analytical processes together in one platform. The study showed that even though the new laboratory performed 17.7% more tests than the old laboratory, it still performed better and more efficiently in all the key metrics:

- % Achievement of TAT goal increased 10.6%
- Working step, personnel, waiting time from phlebotomy room and drawing sample tube were reduced by 70%, 66.7%, 73.3% and 1.6% respectively
- Furthermore, aliquot tip and cup are not required due to the nature of the consolidated platform which has a huge impact in terms of cost saving for laboratory.

27th August 2014 (Wednesday)
1215-1400
Sarawak Room

Lunch Symposium 2: (Sysmex)

Moderator: Lai-Meng Looi

LS2a. Intraoperative molecular analysis of total tumor load in sentinel lymph node: a new predictor of axillary status in early breast cancer patients

Vicente Peg

Axillary staging has been considered as one of the main prognostic factors in breast cancer patients[1,2]. Thus, from the first surgical approaches to this disease, complete axillary lymph node dissection (cALND) was performed in every patient because of its benefits in survival.

The concept of the sentinel lymph node (SLN) was a big change in the surgical management of breast cancer. The possibility of identifying a first station of drainage, which inform about the negativity of the rest of axillary nodes, made possible the reduction of unnecessary lymphadenectomies and the consequent decline of the side effects associated with it such as lymphedema. However, despite the decrease of cALND, there still remained a non-negligible number of patients where the SLN was the only positive node and surgery, therefore, did not seem to offer any benefit. In this sense many nomograms began to be developed to try to identify those patients[3].

Recently published results of the ACOSOG Z0011 trial have meant another radical change[4]. It has demonstrated that there was no difference in overall survival and disease free survival or locoregional recurrence rates between a subset of patients planned for breast conservation therapy including whole breast irradiation with one or two positive SLNs.

The question that arises then seems obvious: what is the meaning of SLN at this point? Why should we still analyze it if it doesn't seem to change the surgical procedure nor the prognosis in a subset of breast cancer patients? And, on the other hand, how would we apply the TNM classification, the "N" in particular, if we do not know the real axillary status since 27% of the patients with positive SLNs had more affected lymph nodes in the Z0011 trial? Shall we better to talk only of N0 and N1 patients, as we do for metastases?

However, even if the study Z0011 was supposed to be "practice changing", there is still a certain reticence in the scientific community in implementing its conclusions. It is widely known that there are some controversies that can be found in this study, on the basis that there where many patients underrepresented. In fact recent publications about changes in the surgical practice after the publication of the Z0011 show that there is still a percentage of patients (around 25%) when, even if they meet the inclusion criteria of the Z0011 trial, axillary clearance is still performed[5,6]. Among the reasons to follow this practice is the use of nomograms that try to ensure that there will not be more positive nodes beyond the SLN.

At this point, what will be the role of SLN? While we wait for new prognostic factors definitive implantation (as the application of gene signatures), axillary status is still an important risk factor. However, all the information we got after analysing multiple nodes must now focus on 1 or 2 in those patients where cALND is not performed.

New technologies are now available for the analysis of SLN, that allow an automated, reproducible and standardized evaluation of the node. We have recently published that the molecular analysis of tumor load by OSNA in the SLN predicts the risk of involvement of further nodes, even better than the number of affected nodes[7,8]. Following this road, could this information help us to better classify patients and treat them accordingly? What is the question that we want SLN to answer? Is it no longer a factor to decide treatment but a prognostic factor than can replace the information provided but cALND?

1. Fisher B, Bauer M, Wickerham DL, et al. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. Cancer 1983;52:1551-7.
2. Michaelson JS, Silverstein M, Sgroi D, et al. The effect of tumor size and lymph node status on breast carcinoma lethality. Cancer 2003;98:2133-43.
3. van la Parra RF, Peer PG, Ernst MF, Bosscha K. Meta-analysis of predictive factors for non-sentinel lymph node metastases in breast cancer patients with a positive SLN. Eur J Surg Oncol 2011;37:290-9.
4. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. Jama 2011;305:569-75.
5. Caudle AS, Hunt KK, Tucker SL, et al. American College of Surgeons Oncology Group (ACOSOG) Z0011: Impact on Surgeon Practice Patterns. Ann Surg Oncol 2012;19:3144-51.
6. Gainer SM, Hunt KK, Beitsch P, Caudle AS, Mittendorf EA, Lucci A. Changing Behavior in Clinical Practice in Response to the ACOSOG Z0011 Trial: A Survey of the American Society of Breast Surgeons. Ann Surg Oncol 2012;19:3152-8.
7. Peg V, Espinosa-Bravo M, Vieites B, et al. Intraoperative molecular analysis of total tumor load in sentinel lymph node: a new predictor of axillary status in early breast cancer patients. Breast Cancer Res Treat 2013;139:87-93.
8. Espinosa-Bravo M, Sansano I, Pérez-Hoyos S, et al. Prediction of non-sentinel lymph node metastasis in early breast cancer by assessing total tumoral load in the sentinel lymph node by molecular assay. Eur J Surg Oncol 2013;39:766-73.

LS2b. Liquid Biopsy: tailored non-invasive testing in oncology

Vishal Sikri

Sysmex Inostics' OncoBEAM™ tests allow for a very sensitive analysis of circulating tumor DNA that is shed into the blood stream. These novel, blood-based liquid biopsies provide a non-invasive alternative to traditional biopsies in determining the mutational status of a patient's tumor. From a clinical perspective, the OncoBEAM™ assays allow for an earlier prediction of targeted drug response in patients by targeting clinically actionable gene mutations in late stage cancers to provide the oncologist with the most appropriate and effective treatment for their patients. The assays can also be used to monitor a tumor's response to targeted therapy or to detect an emerging resistant mutation during treatment.

For the oncologist, the OncoBEAM™ tests reflect the real-time mutation status of a patient. This allows for more timely delivery of targeted therapies for more effective disease management in later stage cancer patients. Sysmex Inostics's believes that to the oncologist, surgeon and pathologist, a blood-based biopsy will be the method of choice in the near future for therapy selection determination. Most importantly, no longer does the patient need to undergo additional tissue biopsies for determining the tumor's status or in measuring the effectiveness of the therapies and treatments.

28th August 2014 (Thursday)
1245-1400
Sarawak Room

Lunch Symposium 3: Concurrent sessions (Novartis/ BD Diagnostics)

LS3a. Novartis
Moderator: Hairuszah Ithnin

The key role of pathologist in improving diagnosis of NETs

Chin-Yuan Tzen

Department of Pathology and Laboratory Medicine, Cathay General Hospital, Taipei, Taiwan

According to the WHO Classification of 2010, gastroenteropancreatic neuroendocrine tumors (GEP-NETs) can be divided into well-differentiated tumors and poorly differentiated carcinomas by cytomorphology of tumor cells, or divided into grades 1, 2, and 3 by proliferative activity of tumor cells. The updated WHO classification is easily understandable and simple to apply because this classification dissociates the diagnosis from the tumor staging, origin, and functioning status. However, uncertainties may happen when cytomorphology gives ambiguous appearance, a liver metastasis is found without knowing the primary site, a symptomatic patient presents an incomplete syndrome, and a somatostatin analogue is prescribed before predicting its effect. Such an uncertainty may affect treatment because not all GEP-NET patients are treated the same way. Therefore, the key role of pathologists is to provide clinically relevant information that discloses the true status of the disease. In this regards, immunohistochemical analysis of MASH and NeuroD is useful for determining the differentiation status of GEP-NETs; that of PDX-1, ISL-1, and CDX2 for tumor origin; that of insulin, gastrin, glucagon, and VIP-1 for functioning status; and SSTR-2 and -5 for responsiveness to somatostatin analogues. These informations are useful for clinical management of patients with GEP-NETs and can only be provided by pathologists, addressing the modern role of pathologists in the era of personalized medicine.

LS3b. BD Diagnostics
Moderator: Zubaidah Abdul Wahab

Better patient management which entails emerging resistance detection and faster turnaround time in the microbiology workflow

David Newsome

BD Diagnostics

Resistance to a variety of antimicrobial agents is emerging in bacterial pathogens throughout the world. Increases in the prevalence of penicillin resistance in Streptococcus pneumoniae, methicillin resistance in Staphylococcus aureus, vancomycin resistance in enterococci, extended-spectrum αlactamase-production in enteric gram-negative bacilli, and fluoroquinolone resistance in Neisseria gonorrhoeaeare are just a few examples of the rising problem of resistance documented by both national and international surveillance systems in the past few years. In view of the prevalence of this happening, it would be vital that microbiology lab is equipped with technologies suitably placed to monitor emerging resistance. Should the medical community look beyond SIR interpretation and have a more thorough investigation of the MIC of the different pathogens/antimicrobials in order to have a more effective antimicrobial stewardship?

Further on to this, should there be an improvement in streamlining of microbiology workflow with efficiency, reduced errors and faster turnaround time to reportable results in mind? In this session, we will discuss what the available solutions are today that will propel microbiology laboratories towards the paradigm shift which will contribute positively to patient management.