Non-invasive Prenatal Diagnosis: From Dream to Reality

Dennis Y.M. Lo
Li Ka Shing Institute of health Sciences and Department of Chemical Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, N.T., Hong Kong.

In 1997, our group discovered the presence of cell-free fetal DNA in the plasma of pregnant women. This finding has opened up new possibilities for non-invasive prenatal diagnosis. Early applications have focused on the detection of paternally-inherited genes or mutations that are not present in the pregnant woman's genome. Over the last few years, much effort has been used for exploring this approach for the prenatal detection of fetal trisomy 21. Our group has pioneered approaches based on fetal epigenetic markers, fetal RNA markers and most recently by massively parallel sequencing. Using massively parallel sequencing, fetal trisomy 21 can be detected with a close to 100% sensitivity and a specificity of 98%. When used as a screening test, this approach has the potential to greatly reduce our needs for invasive testing. Apart from trisomy 21 detection, this approach can be used for the screening of trisomy 13 and 18, and for detecting multiple autosomal genetic diseases.

Linking Cancer Genomics with Patient Management

Edmond S.K. Ma
Department of Pathology, Hong Kong Sanatorium & Hospital, Hong Kong.

Cancer biomarkers have evolved from assays based on proteins, hormones and enzymes to molecular assays based on DNA or RNA. These molecular cancer biomarkers have found broad clinical application in disease diagnosis, classification, prognostication, risk stratification, treatment decision making, monitoring and screening. What matters most to the practicing oncologist is the ability to harness molecular cancer biomarkers to predict treatment efficacy or toxicity in the individual patient, thereby guiding the choice of treatment. The term theranostics is recently coined to indicate this marriage between diagnostic and therapeutics. Of note, before therapeutics can be directly linked to diagnostics, the analytical validity, clinical validity and clinical utility of the test in question should be carefully considered, not to mention the ethical and financial implication. Predictive cancer markers to molecular targeted therapy may be positive or negative. The best known examples of positive predictors are *EGFR* gene mutation in non-small cell lung cancer and *HER2* gene amplification in breast cancer, whilst *KRAS* and *BRAF* gene mutations are negative predictors in metastatic colorectal cancer. Development of molecular cancer biomarkers is no double fueled by the ever expanding repertoire of targeted agents, a recent example being detection of *EML4-ALK* gene fusion for consideration of ALK inhibitor therapy in lung cancer. Apart from the predictor markers, pharmacogenomics is another important facet of cancer theranostics. Notable examples are thymidylate synthase expression or genotype and response to 5-FU and related compounds, ERCC1 expression and response to cisplatin; and *UGT1A1* genotype and irinotecan toxicity. It is envisaged that the emerging diagnostic use in the cancer genome of next-generation sequencing technology to detect mutations and array-based comparative genomic hybridization to interrogate copy number variations will further advance personalized oncology in the future.

Translating the Knowledge on Human Papillomavirus to control Cervical Cancer

Paul K.S. Chan
Department of Microbiology, The Chinese University of Hong Kong, Hong Kong.

In 1970s, Prof. Harald zur Hausen, one of the Nobel laureates in Physiology / Medicine in 2008, raised the hypothesis that human papillomavirus (HPV) is the cause of cervical cancer. After more than 20 years of hard work, a strong body of evidence had been generated and proved that HPV is a necessary cause of cervical cancer. Since 2000s, a substantial progress has been made in translating the basic scientific knowledge to clinical use. For instance, infection with certain types of HPV is now proved to be a clinically useful early marker for cervical cancer screening. In addition, the detection of certain types of high-risk HPV can provide long-term predictive value for stratifying the risk of developing cervical cancer for an individual. These new developments will reform and improve the cost-effectiveness of cervical screening programs. An even more encouraging successful translation is the development of prophylactic vaccines against HPV infection and the subsequent development of cervical intraepithelial neoplasia and invasive cancer. This breakthrough is going to turn cervical cancer control to a new chapter. This talk will cover what have been achieved and what are potential areas for further improvement.

Roles of Medical Laboratory in Providing Translational Cell Therapy

Kent K.S. Tsang
Bone Marrow Transplant Laboratory, Division of Haematology, Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong.

Cells have long been used as adjuvant therapy in addition to primary treatment. Recently stem cell therapy was regarded as a treatment modality for patients with otherwise incurable disease by conventional regimens. Bone marrow transplantation becomes a promising regimen for a variety of life-threatening diseases. With the advent of recombinant technology and the availability of cell separators, haematopoietic stem cells (HSC) are collected from the peripheral blood of patients/donors having undergone cytokine mobilization. Umbilical cord blood are also quality HSC. The manoeuvres of HSC therapy depends much on the innovative laboratory technologies. ABO-incompatibility occurs frequently in HLA-matched transplant. Avoidance of intravascular haemolysis at the time of infusion of major ABO-mismatched HSC products can be achieved by red cell depletion or plasmapheresis of recipients to remove circulating ABO-antibodies to a safe titre. T-cell purging and positive selection of HSC are conducted to alleviate graft-versus-host disease in HLA-msmatched transplants. HSC autografts harvested from tumour-bearing patients at clinical remission may have occult tumour cell dissemination. *Ex-vivo* tumour cell purging is performed to eradicate any residual tumour cells that may attribute to graft-mediated disease relapse upon re-infusion. Positive selection is also an effective means to enrich HSCs and negatively deplete tumour cells in autografts. The discovery of stem cell plasticity raises the hope that non-haematological disorders might become amenable to stem cell therapy to replenish the cell loss and degeneration. Preliminary results of randomized controlled phase-I/II trials of bone marrow-derived mesenchymal stem cells and UCB for stroke and spinal cord injury, respectively, are reported.

Cytogenetic Studies in Non-viable Pregnancies

W.K. Chan, Anna Chan, Andy Suen
The Prenatal Cytogenetic Laboratory, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong.

In an investigation of more than 130 non-viable pregnancies where placental tissues and abortus tissues were studied. There were a lot of abnormal cytogenetic findings amounting to about 47% of the total investigations. 46.3% of samples had no visual cytogenetic abnormalities and 3.7% were not successful in tissue cultures and therefore had no cytogenetic results. Among the abnormal results, 95.2% were aneuploidies. 73% were trisomies, including Trisomy 15, Trisomy 13, Trisomy 9, Trisomy 14, Trisomy 18, Trisomy 22, Trisomy 16, Trisomy 4, Trisomy 2, Trisomy 20 etc. Others involved Monosomy X or Turner Syndrome (11.1%) and 5 cases of polyploidy ranging from hyperdiploidies, triploidy to tetraploidies. Only three cases (4.8%) had chromosomal structural rearrangements. It is interesting to find that trisomies were the most important causes of non-viable pregnancies and this is also related to advanced maternal age due to non disjunction in cell division, especially in meiosis. Chromosomal structural abnormalities were less common in abortions. The chromosome trisomies being found most common in premature foetal death include chromosomes in the order of 15, 13, 9, 14, 18, 22, 16, 21, 4, 1 and 20. We did not find trisomies involving other chromosomes, perhaps normal pairs of these chromosomes would be too vital for normal development of the fetuses. Compared with full term babies identified postnatally to have chromosomal abnormalities, Trisomy 21, Trisomy 18 and Trisomy 13 are the most common which denote that chromosomes 21, 18 and 13 affect foetal development but may not be so serious to cause premature intrauterine foetal death.

Case Study – Ictal Status with Uncommon Etiology

Sydney C.F. Yuen
Institute of Haematology, Royal Prince Alfred Hospital, New South Wales, Australia.

A 15 year male visiting Sydney, Australia from UK as part of the Youth Olympics Diver Team in 2009 had a fit. He was brought in by ambulance to Emergency Dept of Royal Prince Alfred Hospital in Sydney following a witnessed tonic clonic seizures lasting 30 minutes. On arrival in ED, he was tachycardic, hypotensive, hypothermic O_2 saturating at 92% and a petechial rash was noted. A sample of venous blood was sent to Pathology (Haematology, Blood Bank and Clinical Biochemistry). While awaiting results, resident observed his BP dropped further and abdominal distension was evident but EEC was normal. Haemoperitoneum was suspected. An urgent laparotomy was organized and later splenectomy was carried out. The sudden rupture of spleen at one stage would attribute to the prior preparatory training before arriving Sydney. However, with review of blood film suggested the underlying cause is infectious mononucleosis and confirmed by lymphocyte surface marker study on peripheral blood and EBV serology including positive monospot and other tests. Sections of spleen also confirmed that splenic rupture was due to the EBV infestation not trauma. The likely mechanisms of the causes of the disease are also proposed during discussion. The English youth was discharged well after 27 days in hospital and expected to do well. Had this episode happened to him outside a hospital, the chances of saving him would be minimal.