NEWSLETTER OF THE HONG KONG COLLEGE OF PATHOLOGISTS

PATHOLOGUE

The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability

THE HONG KONG COLLEGE OF PATHOLOGISTS
SCIENTIA ILLUMINAT MEDICINAM
香港病理學專科學院

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Message from the President

Dear Fellows and Members,

In this issue of College Newsletter, I have to bring very sad news to all Members and Fellows. Our Past President, Dr. Michael Suen passed away peacefully on 6 January 2020 after battling against cancer for over 2 years. Dr. Suen was a leader with traditional Chinese wisdom, an excellent practising pathologist, a resourceful and encouraging mentor, a good friend with whom you can share your feelings, a caring husband and father. He was a great role model for our community, College, trainees, colleagues and his family members. We will never forget his smiling face and warm words of encouragement, in particular, during times of difficulty. May Dr. Suen rest in peace.

On the other hand, there is a series of good news for our College in the past year.

The breaking good news is the award of Professor Dennis Lo, Li Ka Shing Professor of Chemical Pathology, who was admitted as Honorary Fellow of The Hong Kong Academy of Medicine in December 2019 in recognition of his contribution to the field of cell-free plasma DNA for non-invasive prenatal and cancer diagnostics.

The second good news is the award of Distinguished Young Fellows 2019 to Dr. Elaine Au, Consultant Immunologist and Dr. David Christopher Lung, Consultant Microbiologist. They received the award from Professor CS Lau, Academy President, in September 2019.

The third good news is the successful Membership Examination and Fellowship Assessment for candidates in Anatomical Pathology, Chemical Pathology, Clinical Microbiology and Infection, Forensic Pathology as well as Haematology in August and September 2019.

The fourth good news is the successful completion of the First Fellow Assessment for candidates in Genetic and Genomic Pathology in October 2019.

The College Examinations could not have been successfully conducted without the help of our External Examiners, Chief Examiners and Local Examiners. During the past months of social unrest, some of our External Examiners were not able to come to Hong Kong physically. Tele-communication was adopted to be the alternative option by the College and Academy. Thank you for the hard work and contributions from all examiners.

The fifth good news would be the award of The DS Nelson Trainee Oral Prize to Dr. Timothy Cheng, at the 'Pathology Update 2019' Conference in Melbourne. The title of his presentation was 'Noninvasive Detection of Bladder Cancer by Shallow-Depth Genome-Wide Bisulfite Sequencing of Urinary Cell-Free DNA for Methylation and Copy Number Profiling'.

In this issue, the Topic Update was on "Recent Advances in Acute Lymphoblastic Leukaemia " by Dr. Albert Sin, and the Out of the White Coat Interviewee was Dr. Clarence Lam, Consultant Haematologist.

The International Pathology Day Pre-Workshop was conducted to induce medical students to explore various disciplines of pathology in November 2019. Again due to social unrest, the International Pathology Day was postponed to a Saturday before Christmas when it was successfully conducted at the Pathology Teaching Laboratory of The Chinese University of Hong Kong, Prince of Wales Hospital.

Finally, let me wish all of you a Prosperous Chinese New Year of the Rat!

Dr. CHAN Ho Ming
President

Please send comments to:
Dr. CHEONG Renee Constance Yue-kew,
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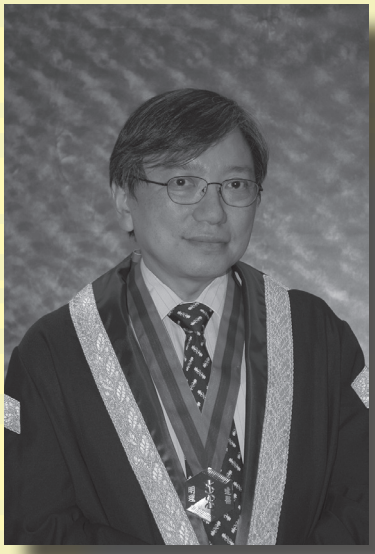
OBITUARY – DR. SUEN WANG MING, MICHAEL

Dr. SUEN Wang Ming, Michael, *passed away peacefully in the arms of his wife on the evening of 6 January 2020, after a courageous battle with cancer. I still remember the first day I met Dr. Suen in his office when I was desperately looking for a Pathology post at the time of economic recession in 2002. Dr. Suen had guided me through my career and witnessed my transformation from a junior resident to a Pathology Fellow, and, following in his footsteps, to a Council Member of our College. In him, I see the caring heart and professionalism of a doctor, the leadership and wisdom of a mentor, and the gentleness and humility of a father and husband. I am so proud and honoured to be associated with Dr. Suen. With kind agreement from Dr. Suen's family, we have prepared his valedictory.*

MAK Siu Ming



Dr. Suen was born in Hong Kong in 1955. He graduated from the Royal College of Surgeons in Ireland in 1981 and commenced his clinical practice at the Caritas Medical Centre. He joined The Chinese University of Hong Kong in 1984, started his career in pathology and took up a teaching role in the medical undergraduate programme. In 1997, he switched to the public health care system, serving as the Founding Consultant and Chief of Service in Pathology Service at Alice Ho Miu Ling Nethersole Hospital. He was also the Cluster Coordinator of the New Territories East Cluster. Dr. Suen had recently retired after a successful career as a Consultant.

During his tenure as College President, Dr. Suen tackled a number of controversial issues and introduced structured molecular training into our training programme, which serves as the foundation for today's Genetic and Genomic Pathology programme. He was also President of the Hong Kong Division of the International Academy of Pathology from 1995 to 1996, and was actively involved in the accreditation of medical laboratories by offering advice to the Hong Kong Accreditation Service.

Dr. Suen was not only a successful leader and pathologist, but also a most caring and friendly person. His open and approachable personality made himself a good friend to everyone. Dr. Suen was always loyal to his friends and willingly offered unconditional support whenever needed. Dr. Suen was an artistic person who was able to see beauty in daily life and was fascinated by photography, movies and music. His desire to "reproduce the original moment" drove him to become an excellent photographer and a serious audiophile. He is survived by his wife, Victoria, to whom he was happily married for 25 years; along with their two daughters, both of whom are continuing his legacy in studying medicine.

Dr. Suen will be deeply missed, and his lovable smile and gentle voice will never be forgotten.

Professor Dennis Lo is awarded Honorary Fellowship of the Hong Kong Academy of Medicine

Our Honorary Fellow, Professor LO Yuk Ming, Dennis, of The Chinese University of Hong Kong, has been awarded an Honorary Fellowship by The Hong Kong Academy of Medicine. Honorary Fellowships of The Hong Kong Academy of Medicine are awarded to persons of eminence or persons who have rendered outstanding service to medical science or to the Academy. Professor Lo was the only nominee of the prestigious title this year and is also the first Honorary Fellow of the College to be given this award. He becomes the 17th Honorary Fellow of the Academy in its 26-year history.

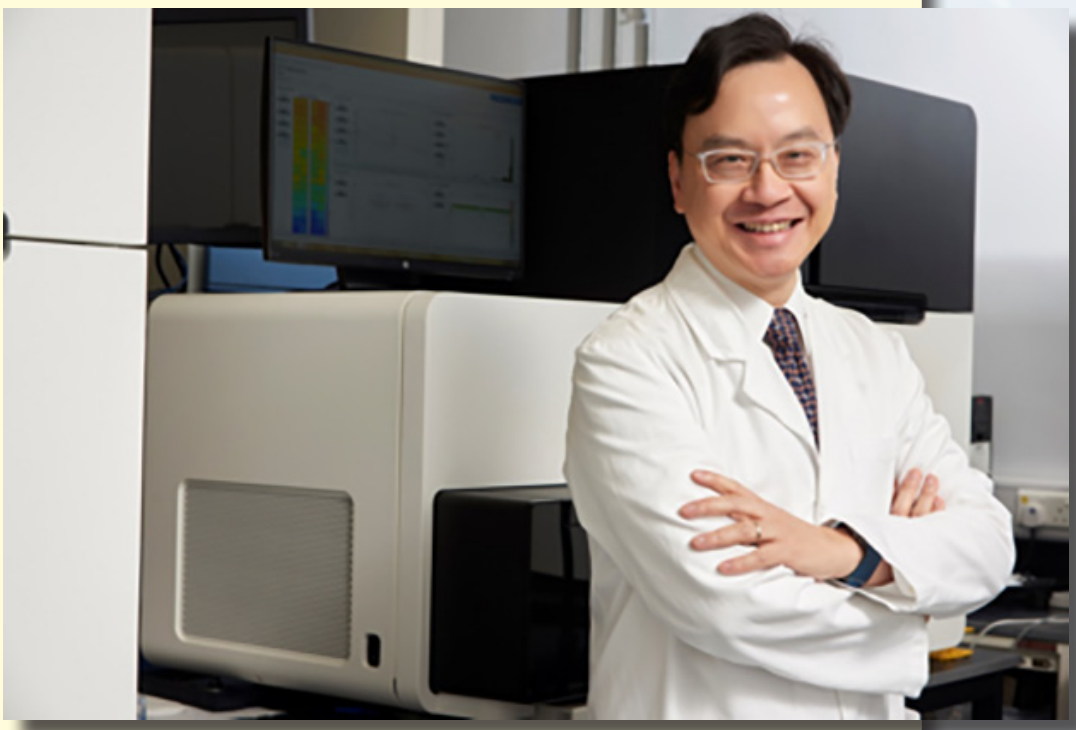
Professor Dennis Lo is the Director of the Li Ka Shing Institute of Health Sciences, the Li Ka Shing Professor of Medicine and Professor of Chemical Pathology of The Chinese University of Hong Kong (CUHK). He is also the Associate Dean (Research) of the Faculty of Medicine of CUHK. Professor Lo received his Bachelor of Arts degree from the University of Cambridge and the Doctor of Medicine and Doctor of Philosophy degrees from the University of Oxford.

Following his training at Oxford, he was appointed as the University Lecturer in Clinical Biochemistry and Honorary Consultant Chemical Pathologist at the John Radcliffe Hospital, the teaching hospital of the University of Oxford Clinical School. He was also a Fellow at Green College, Oxford.

Professor Lo returned to Hong Kong in 1997. In the same year, he discovered the presence of fetal DNA in maternal plasma. His group has since remained at the forefront of this field. His group was the first to report the presence of cell-free fetal RNA and fetal epigenetic markers in maternal plasma and pioneered the use of such markers for noninvasive prenatal diagnosis. Professor Lo and his colleagues were also the first to show that cell-free fetal nucleic acids in maternal plasma could be used for the noninvasive prenatal diagnosis of fetal trisomy 21 and had devised multiple solutions for this hitherto difficult diagnostic problem, including methods based on plasma RNA-SNP allelic ratios, plasma epigenetic markers, digital PCR and massively parallel DNA sequencing. With the use of massively parallel sequencing and the development of novel bioinformatics strategies, Professor Lo's group succeeded at deciphering a genome-wide genetic map of the fetus through the analysis of the small amounts of fragmented DNA floating in the blood of pregnant women. This scientific achievement lays the foundation for developing non-invasive prenatal diagnostic tests for multiple genetic diseases in a non-invasive way.

In the area of cancer detection, Professor Lo has pioneered a number of approaches to cancer liquid biopsy, especially for the detection of nasopharyngeal carcinoma and genome-wide approaches for screening multiple types of cancer.

In recognition of his work, Professor Lo has been the recipient of numerous awards, including the King Faisal International Prize in Medicine in 2014 and the Future Science Prize - Life Science Prize in 2016. He was elected as a Fellow of the Royal Society in 2011, as a Foreign Associate of the US National Academy of Sciences in 2013 and as a Founding Member of the Academy of Sciences of Hong Kong in 2015. More recently, he was named "Top 20 Translational Researchers of 2017" by the authoritative scientific journal *Nature Biotechnology.*



▲ *Professor LO Yuk Ming, Dennis*

Congratulations to our Distinguished Young Fellows 2019!

A total of 26 Distinguished Young Fellows were recognized for their achievements during the Hong Kong Academy of Medicine Council Dinner hosted by President Professor C.S. Lau on 20th September 2019. The Academy President congratulated them on their accomplishments, and encouraged greater engagement in Academy's activities and affairs so as to better understand the Academy's objectives and work.

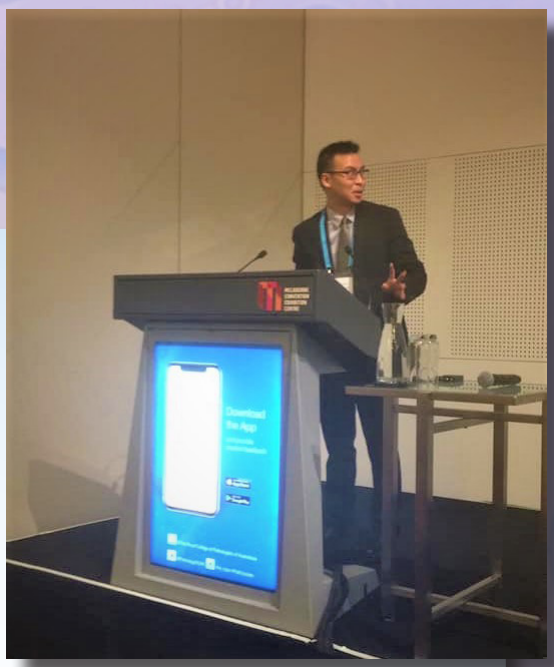
The dinner was also attended by the Academy's Past Presidents, Dr. David Fang, Professor Grace Tang and Professor Raymond Liang, and Honorary Fellow of the Hong Kong Academy of Medicine, Professor Rosie Young. Members of the Young Fellows' Chapter 2019-20 also joined the dinner.

During the dinner, Professor Rosie Young made insightful remarks, which highlighted the importance of nurturing and grooming future medical leaders while striving for excellence in one's own profession.

The dinner concluded with a sharing session by several distinguished young Fellows.

▲ *The President with Distinguished Young Fellows of The Hong Kong College of Pathologists, Dr. AU Yuen Ling Elaine and Dr LUNG David Christopher. Left to Right: Dr. TANG Wai Lun, Dr. LUNG David Christopher, Dr. CHAN Ho Ming, Dr. AU Yuen Ling Elaine, Dr. CHONG Yeow Kuan Calvin.*

The DS Nelson Trainee Oral Prize



The DS Nelson Trainee Oral Prize is awarded annually to the best oral presentation of original research in honour of the late Professor David Selwyn Nelson, a distinguished pathologist whose research covered haematology, Immunology and microbiology. He was also editor of 'Pathology' from 1985-1988. This year, the flagship trainee prize was awarded to our Chemical Pathology Trainee, Dr. CHENG Hua Tse, Timothy, at the Pathology Update 2019 conference in Melbourne. The title of his presentation was **'Noninvasive Detection of Bladder Cancer by Shallow-Depth Genome-Wide Bisulfite Sequencing of Urinary Cell-Free DNA for Methylation and Copy Number Profiling'**.

The article was published in the journal 'Clinical Chemistry' in July this year, with the abstract as follows:

Background: The current diagnosis and monitoring of bladder cancer are heavily reliant on cystoscopy, an invasive and costly procedure. Previous efforts in urine-based detection of bladder cancer focused on targeted approaches that are predicated on the tumor expressing specific aberrations. We aimed to noninvasively detect bladder cancer by the genome-wide assessment of methylomic and copy number aberrations (CNAs). We also investigated the size of tumor cell-free (cf)DNA fragments.

Methods: Shallow-depth paired-end genome-wide bisulfite sequencing of urinary cfDNA was done for 46 bladder cancer patients and 39 cancer-free controls with hematuria. We assessed (a) proportional contribution from different tissues by methylation deconvolution, (b) global hypomethylation, (c) CNA, and (d) cfDNA size profile.

Results: Methylomic and copy number approaches were synergistically combined to detect bladder cancer with a sensitivity of 93.5% (84.2% for low-grade nonmuscle-invasive disease) and a specificity of 95.8%. The prevalence of methylomic and CNAs reflected disease stage and tumor size. Sampling over multiple time points could assess residual disease and changes in tumor load. Muscle-invasive bladder cancer was associated with a higher proportion of long cfDNA, as well as longer cfDNA fragments originating from genomic regions enriched for tumor DNA.

Conclusions: Bladder cancer can be detected noninvasively in urinary cfDNA by methylomic and copy number analysis without previous knowledge or assumptions of specific aberrations. Such analysis could be used as a liquid biopsy to aid diagnosis and for potential longitudinal monitoring of tumor load. Further understanding of the differential size and fragmentation of cfDNA could improve the detection of bladder cancer.

College Examinations

Despite the social events in Hong Kong, the College Fellowship and Membership examinations went ahead according to schedule but not without the assistance of modern technology. The External Examiners for Clinical Microbiology and Infection, and Anatomical Pathology, were unable to come to Hong Kong as planned, so contingency plans were drawn up at short notice and candidates were advised of the new arrangements. The viva examinations were conducted smoothly using teleconferencing facilities at The University of Hong Kong and The Chinese University of Hong Kong.

◀ ***Examiners for Forensic Pathology 2019: from left to right***
Dr. LAM Wai Man
Dr. POON Wai Ming (Chief Examiner)
Dr. Richard Thorley Shepherd (External Examiner)
Dr. LAI Sai Chak
Dr. LAM Wai Kwok

▲ ***Examiners for Anatomical Pathology (Membership Viva) 2019:***
Front row from left to right: Dr. CHAN Ngot Htain Alice, Professor John NICHOLLS, Dr. IP Pun Ching Philip (Chief Examiner), Dr. LAU Lin Kiu.
Back row from left to right: Dr. MAK Siu Ming, Dr. LAM Wing Yin, Dr. TANG Wai Lun Victor
On the screen: Dr Martin YOUNG (External Examiner)

▲ ***Examiners for Anatomical Pathology (Fellowship Viva) 2019:***
Front row from left to right: Dr. YUEN Wah Fun Nancy, Professor John NICHOLLS, Dr. IP Pun Ching Philip (Chief Examiner), Dr. LEUNG Chung Ying
Back row from left to right: Dr. LOKE Shee Loong, Dr. CHAN Chak Lam Alexander, Professor TO Ka Fai
On the screen: Dr Martin YOUNG (External Examiner)

▲ ***Examiners for Chemical Pathology 2019: From left to right:***
Dr. Tai Hok Leung Morris, Dr. YUEN Yuet Ping, Dr. Alan McNEIL (External Examiner), Dr. MAK Miu Chloe (Chief Examiner), Dr. SHEK Chi Chung, Dr. LAM Ching Wan, Dr. TAM Sidney

Announcement

Training and Examinations Committee

Congratulations!!

We are pleased to announce that the following candidates have passed the Fellowship Assessment or Membership Examinations. Congratulations!

CHAN Wing Chai Raymond *(Fellowship Assessment – Anatomical Pathology)*

CHEUNG Ho Kwan Alvin *(Fellowship Assessment – Anatomical Pathology)*

LOK Johann *(Fellowship Assessment – Anatomical Pathology)*

NG Hoi Yan Joshua *(Fellowship Assessment – Anatomical Pathology)*

Wan Judith Vonnie *(Fellowship Assessment – Anatomical Pathology)*

NG Wai Yan *(Fellowship Assessment – Chemical Pathology)*

WONG Chi Kin Felix *(Fellowship Assessment – Chemical Pathology)*

HUNG Ling Lung *(Fellowship Assessment – Clinical Microbiology and Infection)*

ZEE Sze-tsing Jonpaul *(Fellowship Assessment – Clinical Microbiology and Infection)*

KWONG Hoi Yi Joyce *(Fellowship Assessment – Haematology)*

WONG Hung Fan *(Fellowship Assessment – Haematology)*

CHAN Angela Zaneta *(Membership Examination – Anatomical Pathology)*

FONG Tsun *(Membership Examination – Anatomical Pathology)*

HAU Man Nga *(Membership Examination – Anatomical Pathology)*

HO Man Kit *(Membership Examination – Anatomical Pathology)*

LIAO Jiawei *(Membership Examination – Anatomical Pathology)*

MOK Ka Kin *(Membership Examination – Forensic Pathology)*

Announcement from the Training and Examinations Committee regarding the Genetic and Genomic Pathology First Fellow Assessment

We are pleased to announce that the Genetic and Genomic Pathology First Fellow Assessment was completed successfully in October 2019.

The whole exercise can be traced back to the year of 2014, when the College was advised by the Hong Kong Academy of Medicine (the Academy) to consider establishing a training programme for Genetics and Genomics in collaboration with sister Colleges, in keeping with the pace of technology advancement.

A Taskforce on Training in Genetics and Genomics (the Taskforce) was established accordingly, with members including the President, Chairman of the Training and Examinations Committee (TEC), College representatives in the Academy Taskforce on Genetics and Genomics Training, Chief Examiners and Specialty Board Chairpersons in the subspecialties of Anatomical Pathology, Chemical Pathology, Clinical Microbiology & Infection, Haematology, and Immunology; the College Registrar and the TEC Secretary. Various meetings

▲ ***Photo taken on 22 November 2017: Taskforce on Training in Genetics and Genomics.***
Front row; from left to right: Dr. SHEK Chi Chung; Dr. CHAN Yuk Tat, Eric; Prof. CHEUNG Nga Yin, Annie; Dr. CHAN Ho Ming; Dr. CHAN Chak Lam Alexander.
Back row; from left to right: Dr. MAK Siu Ming; Dr. SO Chi Chiu, Jason; Dr. MAK Miu; Prof. KHOO Ui Soon; Prof. CHIU Wai Kwun, Rossa and Dr. LAM Woon Yee, Polly.
Taskforce members absent in the photo (in alphabetical order): Dr. CHOW Yu De, Eudora; Dr. FUNG Sau Chun, Kitty; Prof. HO Pak Leung; Dr. KWOK Siu Yin, Janette; Dr. LEUNG Chung Ying; Dr. MA Shiu Kwan, Edmond; Dr. TAM Sidney; Dr. TANG Wai Lun.

were held, and different proposals were discussed among stakeholders. Forums among various specialties, College Fellows and trainees were organised. Comments and inputs received were integrated when preparing the training programme in Genetic and Genomic Pathology. The training programme was finally endorsed by the College TEC and College Council in January 2018, and subsequently endorsed by the Academy Education Committee and the Academy Council in February 2018 and April 2018 respectively. Finally, the specialist registration in Genetic and Genomic Pathology was also endorsed by The Medical Council of Hong Kong in October 2019.

In the interim period, the Council organised the Genetic and Genomic Pathology First Fellow Assessment (the Assessment). Dr. Michael BUCKLEY from The Royal College of Pathologists of Australasia (RCPA) was invited to be the External Assessor of the Assessment. Dr. Buckley is one of the pioneers in the field of Genetic and Genomic Pathology, and has been working in this area for more than 15 years. He has been the President of Human Genetics Society of Australasia (HGSA) (2017-2019). He was the Chief Examiner in Genetics of RCPA in 2002-2009 and the Chief Examiner in Molecular Genetics of HGSA in 2007-2008. He is an experienced pathologist in the field of Genetic and Genomic Pathology and also an experienced examiner in this aspect.

▲ ***Photo Taken 10th October 2019: Genetic and Genomic Pathology First Fellow Assessment Panel members:***
Front row from left to right: Dr. SO Chi Chiu, Jason ; Dr. IP Pun Ching, Philip; Professor CHEUNG Nga Yin, Annie; Dr. Michael BUCKLEY (External Assessor); Dr. CHAN Chak Lam, Alexander
Back row from left to right: Professor HO Pak Leung; Dr. MAK Miu; Dr. CHAN Ho Ming; Dr. WONG Lap Gate, Michael (Convenor); Dr. MAK Siu Ming (Secretarial support); Dr. POON Wai Ming; Dr. CHAN Yuk Tat Eric

The assessment was conducted and completed in October 2019. Due to the social unrest, Dr. Buckley participated via tele-communication for part of the assessment. A total of 101 First Fellows were eventually admitted by the College Council. Our First Fellows would create the momentum to advance the progress in the field of Genetic and Genomic Pathology, not only in Hong Kong, but also worldwide.

Recently, the Government of the Hong Kong Special Administrative Region has recognised the importance of the field of Genetic and Genomic Pathology. Consultations with our College Fellows are being conducted and we believe that the practice in Genetic and Genomic Pathology will become more and more important in the days to come.

The Training and Examinations Committee would like to take this opportunity to express our heartfelt thanks to the External Assessor, Dr. Michael BUCKLEY, the Taskforce members, the Assessment Panel members and all of the people who have given valuable advice and input in the whole process. Without your effort, we would not have succeeded in the establishment of the training programme in Genetic and Genomic Pathology. Now that the admissions process for First Fellows has been completed, details regarding the introduction of the programme will be announced in due course.

▲ *Photo taken on 26 October 2019: Genetic and Genomic Pathology First Fellow Assessment Panel members; this time with Dr Buckley participating in the assessment via tele-conferencing. (Absent from the photo: Prof. HO Pak Leung)*

THE HONG KONG COLLEGE OF PATHOLOGISTS:

TOPICAL UPDATE

Editorial note: *In this topical update, Dr Albert Sin reviews recent advances in diagnosis and management of acute lymphoblastic leukaemia (ALL). We welcome any feedback or suggestions. Please direct them to Dr Rock Leung (e-mail: leungyyr.ha.org.hk) of Education Committee, the Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals and are not necessarily those of the Hong Kong College of Pathologists.*

Volume 14, Issue 2 August 2019

The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability

Recent Advance in Acute Lymphoblastic Leukaemia

Dr. Albert Sin
Clinical Assistant Professor

Acute lymphoblastic leukaemia (ALL) is an aggressive and highly fatal malignancy resulting from clonal mutations of lymphoid progenitor cells. The incidence of ALL is the most common in childhood and age after 50.18 The prognosis of childhood ALL is good with long-term survival rate approaching 90% treated by intensive chemotherapy.[12] Although the incidence of ALL is less in adolescent, young adult as well as adult, the prognosis of ALL in those people is very poor, with only 30-40% of adult patients able to remit.[18] According to the data from US database which registered all patients with diagnosed ALL from 2000 to 2007, the survival rate was 75% at 17 years old, 45% at 20 years old and 15% at 70 years old.[14] An increasing knowledge of disease biology of ALL transformed into insights for development of novel therapies to improve the treatment outcome of ALL.

One of the reasons of adverse prognosis in adolescent and young adult (AYA) as well as adult patients is that they commonly harbored poor-risk genetic aberrations while less patients carried favorable genetic lesion.[14] This could explain the sudden drop in survival from 17 years old to 20 years old.

Ph-like ALL

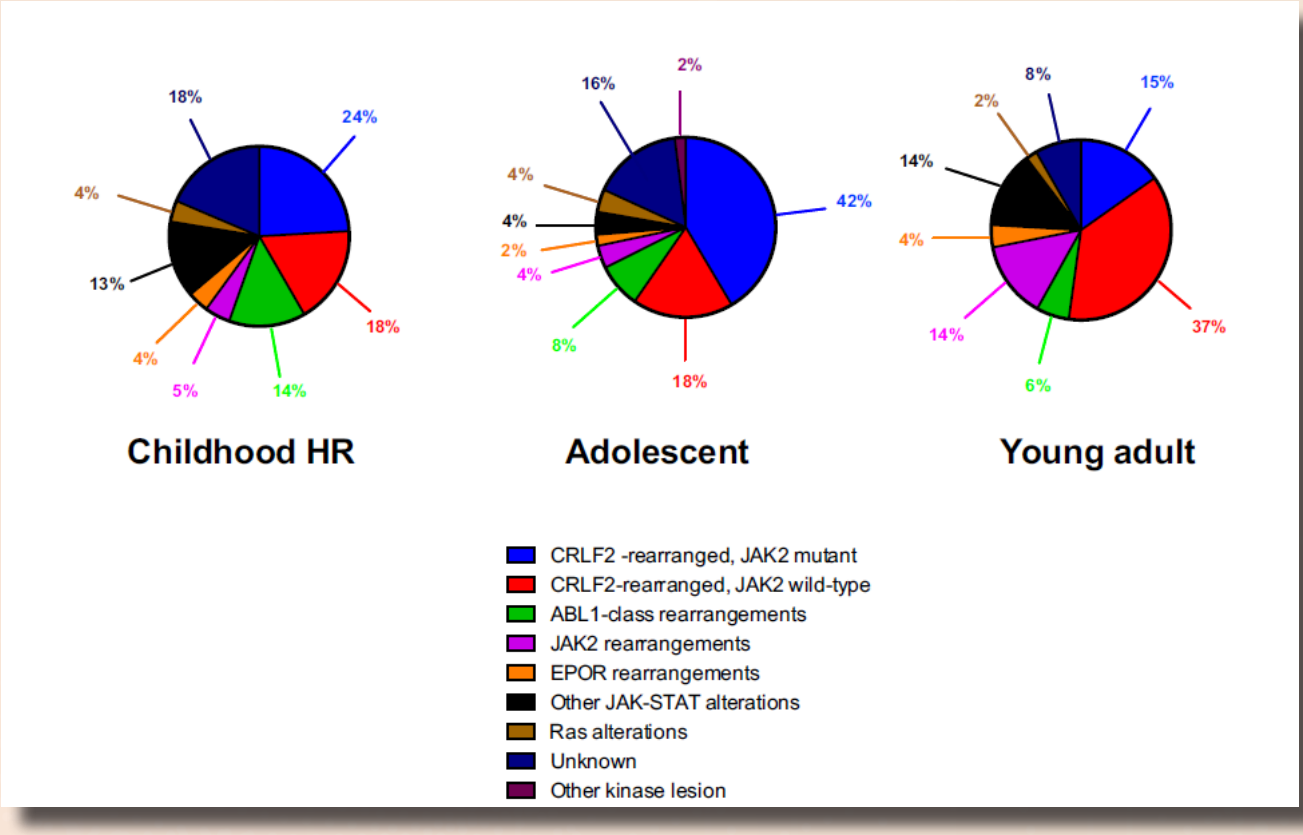
Ph-like ALL is a newly identified genetic subgroup. The genetic profile of this subgroup of ALL is similar to that of Philadelphia chromosome positive (Ph-positive) ALL but without BCR-ABL1 fusion.[17] They have a higher frequency of IKZF1 deletion and mutation in genes of lymphoid transcription factors with poor survival.[19] The incidence of Ph-like ALL increases with ages and approaching 27% of cases of adult B-ALL.[14]

The nature of genetic aberration is heterogeneous. Despite its complexity, it can be simply classified into five subgroups: 1. CRLF2 rearrangement 2. Rearrangement of ABL-class gene 3. Rearrangement of JAK2 and EPOR 4. Aberrations leading to activation of JAK-STAT or MAPK pathway 5. Other rare kinase alterations.[19] The distribution of different types of genetic alterations are different among childhood high risk ALL, young adult and adult (Figure 1). CRLF2 rearrangement is the most common type of genetic alteration in Ph-like ALL. CRLF2 gene is responsible for producing lymphopoietin receptor and regulate the process of lymphopoiesis. Common mechanisms of CRLF2 rearrangement include 1. Translocation of CRLF2 gene into IGH gene 2. Fusion between CRLF2 gene and P2RY8 gene. 3. Point mutation F232C at CRLF2 gene. Nearly 50% of CRLF2 rearranged Ph-like ALL have concomitant JAK mutations.[19]

Diagnosis of Ph-like ALL

Genetic profiling is the gold standard for the diagnosis of Ph-like ALL. However, it is difficult to implement in routine diagnostic laboratory.

Cytogenetics analysis is a standard test for all cases of ALL which allows a global assessment of chromosomal abnormalities. Some of the recurrent genetic abnormalities,



▲ *Figure 1*

Table 1. Repertoire of kinase rearrangements in Ph-like ALL along with their partner genes and potential therapeutic targets

Kinases	5′ partner genes (number of patients)	Potential TKI	Clinical trials
ABL1	*ETV6* (3), *NUP214* (6), *RCSD1* (1), *RANBP2* (1), *SNX2* (1), *ZMIZ1* (2)	Dasatinib	AALL1131
ABL2	*PAG1* (1), *RCSD1* (4), *ZC3HAV1* (2)	Dasatinib	AALL1131
PDGFRB	*EBF1* (6), *SSBP2* (1), *TNIP1* (1), *ZEB2* (1)	Dasatinib	AALL1131
CSF1R	*SSBP2* (4)	Dasatinib	AALL1131
CRLF2	*IGH* (19), *P2RY8* (11)	Ruxolitinib	AALL1521
JAK2	*ATF7IP* (1), *BCR* (2), *EBF1* (1), *ETV6* (2), *PAX5* (7), *PPFIBP1* (1), *SSBP2* (2), *STRN3* (1), *TERF2* (1), *TPR* (1)	Ruxolitinib	AALL1521
EPOR	*IGH* (7), *IGK* (2)	Ruxolitinib	AALL1521
TSLP	*IQGAP2* (1)	Ruxolitinib	AALL1521
IL2RB	*MYH9* (1)	JAK1/JAK3 inhibitor	N/A
TYK2	*MYB* (1)	TYK2 inhibitor	N/A
NTRK3	*ETV6* (1)	Crizotinib	N/A
PTK2B	*KDM6A* (1), *STAG2* (1)	FAK inhibitor	N/A
DGKH	*ZFAND3* (1)	Unknown	N/A

▲ *Table 1*

for example t(9;22), hyperdiploidy/hyperdiploidy, rearrangement involving 11q23, etc, can be detected. However, most of the Ph-like ALL genetic alterations are cryptic, e.g. interstitial deletion of CRLF2, ETV6-RUNX1 fusion, etc and thus they cannot be detected by conventional cytogenetics.[2]

Fluorescent in-situ hybridization (FISH) can be utilized to detect Ph-like ALL genetic abnormalities. Breakapart probes targeting genes most frequently genes including ABL1, ABL2, PDGFRB, JAK2, CRLF2, and P2RY8 are currently available. Although the positive result upon FISH study needs additional fusion probe for confirmation, it provides a readily available and useful diagnostic tool for establishing the diagnosis of Ph-like ALL. However, some of the important Ph-like ALL genetic rearrangement including intrachromosomal inversions (e.g., inv(9) resulting in PAX5-JAK2 fusion), intra-chromosomal deletions (e.g., del(X)(p22p22)/del(Y)(p11p11) resulting in P2RY8-CRLF2 fusion) are undetectable by FISH technique.2 Targeted sequencing

by NGS platform is an evolving technique for diagnosis.[16]

Recently, antibody against CRLF2 is available for flow cytometry study. The expression of CRLF2 as detected by multiparametric flow cytometry is correlated with genetic testing for CRLF2 rearrangement.15 This provides a rapid tool for identifying potential cases of Ph-like ALL before the result of genetic tests is available.

Most of the genetic alterations of Ph-like ALL are targetable kinase lesions, which could be treated by tailored kinase inhibitor therapy (Table 1).[19] This approach of therapy is current undergoing extensive preclinical studies.[9]

Early T-cell precursor ALL (ETP-ALL)

ETP-ALL is recently characterized subtype of T-ALL. It constitutes around 12% of childhood ALL and 7.4% of adult ALL.[11] Genetic profiling showed ETP cells are similar to that of haemopoietic stem cells and myeloid progenitor cells.[4] This subgroup of ALL is characterized by the unique immunophenotype: cytoplasmic CD3+, surface CD3-, CD1a-, CD2-, CD5 dim (<75% positive), CD7 and positive for one or more stem cell and/or myeloid markers including HLA-DR, CD13, CD33, CD34, or CD117.[5]

While activating mutation of NOTCH1 is a common mutation found in ALL and it account for 50% of cases of childhood ALL, this mutation is less common in ETP-ALL.3 ETP-ALL commonly have mutations in FLT3, DNMT3A, IDH1, IDH2, etc.[11]

ETP-ALL carries a poor prognosis with inferior overall survival when treated with standard chemotherapy regimen comparing with other subtypes of T-ALL.[11] This subgroup of T-ALL represented a distinct subtype with unique genetic profile and poor prognosis.

MRD in adult ALL

Minimal residual disease (MRD) describe the very low level of disease burden which cannot be detected by morphology. Measurement of MRD not only pick up a submicroscopic level of disease but also can monitor the disease kinetic during the treatment process of haematological malignancies.[10]

The following techniques can be used to detect MRD:

1. **Multiparametric flow cytometry to detect leukaemia-associated immunophenotype (LAIP)**
   By using a 4-color or 6-color panel of antibodies, we can identify LAIP in 90% of ALL caes.10 Flow cytometry is a quick method and the result of MRD can be generated in a short period of time for clinical decision. The sensitivity of MRD detection by this method is 0.01%. However, in order to define the positive MRD, we need 10-40 cluster of cells and thus higher number of cells are required for assessment which may be difficult for reassessment samples after intensive chemotherapy.7 In addition, antigenic shift is commonly occurred in leukaemic cells and normal cells during the therapy. The use of monoclonal antibodies, e.g anti-CD19, anti-CD22 for treatment of ALL will affect the gating strategy used to identify the leukaemic cells.[10]

2. **Detecting leukaemia-specific fusion transcript by PCR technique**
   Quantitative reverse-transcriptase PCR can be employed to detect the amount of leukaemia-specific fusion transcript. The sensitivity is higher compared with flow cytometry (10^{-4} to 10^{-6}).[7] The test is relatively easy to be performed in standardized diagnostic laboratory. However, only 30-40% of cases of ALL carry leukaemia-specific fusion transcript and thus limited the eligibility of MRD detection by this method. Moreover, the interpretation is challenging for RNA-based test in those cases will poor RNA quality.

3. **Quantitative PCR for immunoglobulin (IG)-T cell receptor (TCR) gene targets**
   Quantitative PCR is employed to detect the specific sequence of rearranged IG gene or TCR gene in the sample. The sensitivity of this method is 10^{-4} to 10^{-5} and this method can be applied to all cases of ALL. However, this method of MRD detection requires prior characterization of IG or TCR gene rearrangement by sequencing and designs patient-specific primers for each case for subsequent MRD detection. Extensive standardization and experience are needed for the laboratory to set up this test, which limit the use of this method of MRD detection in diagnostic laboratory. Moreover, the clonal evolution in leukaemic blasts during treatment can make the original rearranged sequence to be lost and thus generate a false negative result. Also, the non-specific primer annealing occurs during the process of marrow regenerative may yield false positive result for the test.[7]

Application of MRD in treatment of adult ALL

MRD-guided therapy had been gained extensive experience in childhood ALL.[8] The study group of German Multicenter Study Group for Adult ALL (GMALL) had conducted largest study for the role of MRD in adult Ph-negative ALL. They showed that molecular remission is the

only parameters significantly affect the remission duration and survival.[6] Patients with positive MRD after induction therapy achieved better overall survival after receiving haemopoietic stem cell transplant. Early achievement of MRD negativity after induction chemotherapy is associated with good outcome for adult ALL.[10] Study showed that MRD level correlates with post-transplant outcome.[13] Another group found that haemopoietic stem cell transplant benefits the patients with positive MRD at week 6.[1] These findings may prompt reconsideration of the indications of haemopoietic stem cell transplant for adult patients with ALL, especially those patients achieve MRD negativity after treatment.

Concluding landmark

The prognosis of acute lymphoblastic leukaemia in young adolescent and adult is poor. The recent discovery of new subtype of acute lymphoblastic leukaemia with characterization of genetic lesions make a breakthrough of understanding of disease biology. Precise disease prognostication can be made. Targeted therapies are being developed for treating those patients. Clinical trials are conducting for evaluating the targeted therapies in those new subtypes of acute lymphoblastic leukaemia. Moreover, the application of MRD monitoring and MRD-adapted therapy in adult ALL can further stratified the patients and select the appropriate candidates of haemopoietic stem cell transplant in order to reduce transplant-related mortality and morbidity. The advances in understanding of molecular mechanism and disease biology of ALL help to improve the risk stratification, rapid development of targeted therapies and hopefully improve the prognosis in young adolescent and adult patients.

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Out of the Whitecoat:

An interview with Dr. Clarence Lam

Those of us who have worked or rotated to the Division of Haematology at Queen Mary Hospital since the mid-1990s would have been amazed by the forceful symphonies and Soprano high notes while we were looking at our bone marrow slides. These classical music and opera pieces came from the office of Dr. Clarence Lam (CL), who is well known to have a passion for these art forms. Dr. Rock Leung (RL) and Dr. William Choi (WC) recently conducted an interview with Dr. Lam who is very kind to share with us his love of classical music and opera.

RL: Why do you like to play classical music while at work?

CL: I found it easier to concentrate at my work when there is classical music playing in the background.

RL: When did you start to like classical music?

CL: I have always loved classical music since my childhood.

WC: Do you remember which particular work was the one you first contacted?

CL: I really forgot. I could only remember that the prelude was played by a violinist and it was impressive and immediately attracted my attention.

RL: Have you tried to learn musical instruments because of this attraction?

CL: Back in those days, I could only afford to access classical music through listening to radio programmes.

WC: Was it from RTHK4?

CL: No, those days predated the establishment of RTHK4! Those were other radio programmes. It was not until after I have started working when I could build up my collections of audio cassettes, which in a few years' time, were substituted by compact discs.

RL: Which composer does you like the most?

CL: I like Beethoven the most because of his rhetoric and the rebellious and betrayal emotions in his work. I found these elements irresistible as you cannot get them from other composers. Beethoven's later work is particularly unique, as he was already completely deaf. He was basically composing totally in his mind and those last Symphonies by him were just heavenly.

RL: Is there any shift in your preference throughout your life?

CL: No I have been very consistent. Beethoven has always been my favourite composer, but I also like Mozart and many others. For Beethoven, I like his piano sonatas, Symphony No. 9 and Mass in C Major, Op. 86.

WC: Have you thought of studying music instead of medicine since you like music so much?

CL: Today, maybe only a couple of students do not know how to play the piano, but when I was young, only a couple of classmates in the whole class might be able to afford to how to play! So learning music was rather exclusive in the old days.

WC: So when did you learn how to play the piano?

CL: I did not formally learn how to play actually. I like art in general, but music is the most favourite art forms I would say because it is most accessible. For music I just basically need a compact disc and a disc player, but for painting, which is what Rock is practicing, would need a lot of tools and to go to museums to see others' paintings etc.

WC: What was the first compact disc you bought?

CL: It was actually an audio cassette but not a compact disc!

WC: Do you still keep it?

CL: Not any more. I still remember it was a Piano Concerto cassette by Arthur Rubenstein, when I was a Riccian in Medical School. After I started working, we have entered the compact disc era and so I switched to purchasing compact discs. I remember I could buy a stack of compact discs each week…

WC: A stack should mean at least 20 compact discs.
CL: Yes, around 20 something perhaps.

RL: How much was it going to take?
CL: I remember I spent around 7,000 dollars a month on compact discs in the early 90s.

RL: So that means a significant proportion of salary invested in music!
CL: Absolutely!

RL: It is interesting! So you jumped directly from audio cassettes to compact discs?
CL: Vinyl records are in the same period of audio cassettes. And vinyl records require more investments like a vinyl record player and the amplifier system. Audio cassettes you just need to buy an audio cassette player.
WC: Audio cassette is classic!

RL: From your experience, what angle will you advise to one who is not familiar with classical music to appreciate classical music?
CL: I would advise one to just 'go by your heart', as everyone will have his or her own preference. For instance, a friend told me Tsaichovsky's music is very easy to listen to, yet another friend said it does not matter whether the music was composed in a complex way or not, all it matters is whether it is comfortable for most people to listen to. I also have personally recommended Mozart's music to one who was unfamiliar with classical music, but the response was that Mozart's music was 'extreme' in terms of the changes in intensity and the rhythm. So it is hard to do any real recommendations as different people have different preferences. That is why we just need to 'go by our hearts'. If you find it comfortable to listen to the music of a particular composer, you should just go by it.

RL: What about the performers? Do we need any practice to learn how to appreciate the performance of different performers?
CL: I think we do not need any formal practice. When your experience grows, sooner or later you will be able to figure out your own path. It is just like when you grow older and have tasted more restaurants in town, you would know which dish is particularly good in which particular restaurant. And again, there is also an element of 'going by your own hearts'. Some people may say certain pianists or certain conductors are superb but you may not be able to feel it that way.

RL: Why do you like to play music at work? Is it a must and is there a particular reason?
CL: It is not a must for me to play music while working in the office. But certainly it will make working much more enjoyable and less dull.

RL: Do you listen to music at home these days? I know you used to listen to the entire Ring Cycle of Wagner when you were on vacation at home.
CL: Not any more…

WC: You don't want to disturb your daughter?
CL: No. It is just that my preference is a bit different from my wife's. My wife also likes Mozart and Beethoven, but at times I may listen to the works of other composers, which are not her cups of tea. And some operas are boring to my wife and my daughter. So I just leave most of my listening to my work time.

RL: Let's switch topic a little bit. What is the difference between classical music and opera? Did you develop an interest to both at the same time or at different times?
CL: Basically I started to like both at the same time. I actually like listening to people singing since very young and I actually joined choir when I was in school as a kid. So it is natural for me to move into the area of choral music and opera. And a friend told me it is more 'cost effective' to go to a theatre for an opera than to a classical music concert because there are many more to see, including the costumes, the performance of the actors, and the theatrical scenery etc. But this is the reason for me.

WC: What is your one most favourite opera?
CL: It is a tough choice. I would pick Wagner's Tristan und Isolde.

WC: What is the story about?
CL: Tristan was commanded to take Isolde to marry King Marke. They had previously fallen in love with each other already. Later on, after Isolde married King Marke, Tristan and Isolde met secretly but were discovered by the King. Tristan was mortally wounded

and later died in the arms of Isolde. The story is old fashioned but the music is wonderful.

RL: Is it harder to be an opera lover in Hong Kong than in Europe?

CL: To certain extent yes. I used to travel a lot to go see operas. But I seldom do this anymore.

RL: Is it because your daughter is still young? Maybe you can fly more often later?

CL: I guess I am becoming less 'fanatic' in going to theatres to see operas. Some of my friends are having the same pattern as life may have become busier, but there are also others who are flying out to see more often. For me, there are more options now as there are good blue ray DVDs and even cinemas broadcasting live performances. In fact, operas are now much much more accessible in Hong Kong. In the past, there is only one production annually during Hong Kong Art Festival. Now we have several productions each year…

WC: Like the French May…

CL: Yes, French May is one of them as it must contain one French opera. The first time I saw an opera was in the first year of my medical school in City Hall. It was La bohème and I fell asleep in the fourth Act. I don't know why but it was a bit a shame but it shows that for opera it did take me some time to build up the interest.

RL: Have you learned how to sing opera?

CL: Actually yes. My teacher was the father of cantopop singer-songwriter and actress Ivana Wong. He was indeed a tenor and his wife a soprano. They were actually amateur concert performers. Their teachers were one of the earliest sopranos in Hong Kong called Ms. Kong Wah.

RL: When did you learn? When you were in medical school?

CL: After I graduated.

RL: Why did you stop learning?

CL: No time to practice. It really took time to practice.

RL: What did you actually learn to become?

CL: I learned to become a tenor. I really needed to practice. I just learned for 6 months but already found myself having no time to practice.

RL: It really sounds like you were really interested to learn.

CL: Yes. But then I found out that it is easier to listen to others sing as I didn't have to spend so much time practicing.

RL: It really takes a lot of effort.

CL: Yes every skill needs practice. Just like being a haematologist you also need to see a lot of specimens.

RL: This is very true.

WC: It seems that a lot of records stores have closed recently…

CL: Yes, Hong Kong Records have closed.

WC: Yes what is your view on this? I know you have an iPod. Do you purchase and download digital music?

CL: You know I only read physical books but not digital books. For us being more senior in terms of age, we like the tactile sense offered by the very objects. But the problem that comes with physical records is the storage issue. People keep telling me that even if I buy compact discs, I can download the music into the hard disc and then get rid of the compact discs and the cases. But obviously I have not done that.

RL: I personally think it might be less convenient to store it digitally compared with physical discs?

CL: Really? When your collection reaches the size of mine you will know how 'inconvenient' it can be to find a particular disc.

RL: Some discs are being hidden and could not be found…

WC: It would be very painful when moving home.

CL: Yes very painful. I already threw away most of the discs' plastic cases and the booklets, and just put the discs inside large disc holders.

WC: Now that there are fewer records stores, do you buy the compact discs online?

CL: No I still go to a record store which I go to exclusively. I do not go to the large chains like the HMV. I go to a particular one called Percival Records Co. on Wing Kut Street. I have purchased records there for 30 years. Now there are not many that I have not purchased. If there is something that I really want to buy and they do not have it, they can help me order it from overseas.

WC: Do you actually remember what you have purchased?

CL: My principle is if there is any uncertainty, I would not go ahead to purchase. This principle works quite well. There have only been a few instances that I purchased the same record repeatedly.

RL: That is amazing.

CL: But now it is also hard to really check whether I have purchase the same record repeatedly.

RL: Are you able to find out a particular record?

CL: Eventually I think I would be able to. Theoretically, I should be able to find, but it all depends on how, where and how long would it take to find out one particular one.

RL: Maybe it is easier to just purchase one more copy. But some may not be purchased again?

CL: Yes, some may not be purchased again. I also have some that are infested by molds.

WC: Those are audio cassettes?

CL: No. Even compact discs! My previous home was really humid.

WC: Is it ok to just wipe off the molds for compact discs?

CL: Yes it is ok after cleaning. But sometimes the infestation is just too heavy and wiping cannot remove them all. These I can just let them go. I tell myself I have already listened to them so it is worth it already. But sometimes there are also ones that I have not even listened to.

WC: Sounds like books, which some are just being kept on bookshelves…

CL: Yes, not some but most of my books are like that too.

RL: Are there ones that you like you would make it more accessible?

CL: Not necessarily. Sometimes I just purchase another copy knowingly if I cannot find one that I really want to listen to. But knowingly or not, I seldom buy redundant copies, because I have friends that I can borrow ones that I do not have.

The interview was conducted on a beautiful afternoon while we were having our lunch in a cozy restaurant in Kennedy Town. Unwittingly, we followed Dr Lam into the wonderland of classical music and opera. At the end of the interview, we could almost hear the whispering of the heavenly sound of music from the old masters.

Pre-Workshop for the International Pathology Day Workshop 2019

A pre-workshop for the International Pathology Day Workshop (IPDW) was organized on 7 November, 2019 at the Cytogenetics and Genomic Laboratory in Queen Mary Hospital, to induce our medical student helpers from The University of Hong Kong and The Chinese University of Hong Kong.

Fellow pathologists from different disciplines shared with our medical students about the role of pathologists in diagnostics and patient management. A laboratory tour was organized to show them the operation of the clinical laboratory and how modernisation of laboratory medicine and advanced genomic testing help to bring a better future for our patients.


Postmortem Changes


What does Clinical Micr
and Clinical Microb
Specific
Global


Drug of abuse


NK Cell
Cytotoxic T Cell
Helper T Cell
Follicular Dendritic Cell
Macrophage
Treg
B Cell
Plasma Cell
Mast Cell
Basophil
Neutrophil
Eosinophil

Adjustment of Entrance and Annual Subscription Fees from 1st January 2020

The College Council proposed an increment in the College Subscription Fees which was endorsed at the Annual General Meeting held on 23 November 2019. This increment is the first in many years and is effective from 1st January 2020. This increment will support increasing costs incurred from secretarial and other external sources of support that are needed during the College Examinations and Events.

Membership Category			**Subscription**	
Entrance			**Annual**	
	Current	From 1 Jan 2020	Current	From 1 Jan 2020
Honorary Fellows	Nil	Nil	Nil	Nil
Founder Fellows*1,*3	N/A	N/A	$2,400	$3000
Fellows*2,*3	$2,400	$3000	$2,400	$3000
Overseas Fellows*3, *4	$2,000	$3000	$1,000	$1500
Members	$1,000	$1500	$1,000	$1500
Associates	Nil	Nil	$500	$800

Remarks:

\# The date of payment of annual subscription would be every 1st of January.

\# If the date of admission to membership is within 6 months from the coming 1st of January, only half of the annual subscription would be required for this period.

\# On change in the category of membership, payment of the balance of the annual subscription would be required.

*1 For Founder Fellows residing overseas, the annual subscription would be HK$1,000. On residing in Hong Kong for more than 3 months, the annual subscription would be reverted back to the annual subscription of Founder Fellows.

*2 For Fellows residing overseas, there would be no reduction of annual subscription. Fellows residing overseas can apply for changing their category of membership to Overseas Fellows (this category has no voting right).

*3 For Founder Fellows, Fellows and Overseas Fellows with Retired Fellow Status as recorded in the College Register, the annual subscription would be HK$1,000 before 1st of November 2006. Afterwards, only a nominal annual subscription of HK$100 would be applied. Fellows concerned must inform the College immediately should there be any change of their retired status and the reduced rate will cease to apply thereafter. Please refer to the form for "Application for Change of Fellowship Status" for the rights and privileges of Fellows with retired status.

*4 For Overseas Fellows residing in Hong Kong for more than 3 months, the annual subscription would be reverted back to the annual subscription of Fellows.