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

VOLUME 26, ISSUE 2 NOVEMBER 2017

INDEX

Message from the President

Four years ago, I took up the challenging post of President of The Hong Kong College of Pathologists. It is time to pass the responsibility to my capable successor after the AGM this year.

The College has faced challenges while trying our best to achieve the most important mission of safeguarding the quality of training and ensuring high standard of pathology service to our community.

With the aging population and various factors, the demand on medical care in Hong Kong has been increasing. It is known that the majority of clinical decisions need the support of medical laboratory investigations. The opinions of pathologists are crucial in the prevention, diagnosis, and treatment of disease.

Indeed, The Hong Kong College of Pathologists is getting more and more represented in various task forces and specialists panels involved in health care, contributing our professional opinions.

Since the establishment of International Pathology Day in liaison with international pathology community, the College has been organizing an annual workshop for secondary school students. It is our target to let the general public know more about our profession and appreciate our contribution, and to attract potential trainees to our profession.

Thanks to the joint effort of various specialties in Pathology, we are now at the final stage of establishing a post-specialty fellowship in Genetic and Genomic Pathology. This is an important move to face the increasing application of such knowledge in different facets of medicine.

Better planning of manpower and succession is important in the provision of reliable medical services. The Academy and our College hopefully can play more active roles in this aspect.

This season of examination has recently been concluded. A new generation of specialist pathologists is born. On behalf of the College, I would like to extend my sincere welcome and congratulations to all new Fellows and Members. More importantly, I also wish to applaud to all trainees who have bravely endured the serious training and examinations, irrespective of the results. We should also thank all the trainers for their dedicated supervision, and the families of our trainees and Fellows for their continuous support.

Last but not least, I would like to thank all members and friends of the College for your support to College activities. The active participation from our new Fellows is particularly welcome to ensure the success of our profession in serving the community.

Professor CHEUNG Nga Yin, Annie
President
November 2017

Please send comments to:
Dr LAI Sai Chak
(Chief Editor),
Address: *Forensic Pathologists' Office, 6/F Arsenal House West Wing, Police Headquarters, Arsenal Street, Wanchai, Hong Kong.*
E-mail: *sc_lai@dh.gov.hk*
Phone: *2860 2461*
Fax: *2804 1714*

President's activities

▲ *The President attended the International Liaison of Pathology Presidents (ILPP) meeting on 7-9 June and the Annual Meeting of The Canadian Association of Pathologists – Association Canadienne des Pathologistes (CAP-ACP) held on 10-13 June in Charlottetown, Prince Edward Island, Canada.*

▲ *In the CAP-ACP annual meeting the President took part in a debate! The topic was "Given the increasing workloads in Pathology, be it resolved, non-Pathologists such as Pathologists' Assistants and Technologists should report/sign out pathology cases" and she was in the opposing team. Her teammate was Dr Suzy LISHMAN (2nd from right), President of Royal College of Pathologists (RCPath). Dr Bruce LATHAM (first from left) and Dr Michael HARRISON (2nd from left), Vice President and President of the Royal College of Pathologists of Australasia (RCPA) respectively, were the affirmative team. Dr Victor TRON (centre), President of Canadian Association of Pathologists (CAP-ACP), chaired the session.*

▲ *Council members receiving a visit by President of Hong Kong Academy of Medicine, Professor LAU Chak Sing (front row, centre), and other office bearers of the Academy, in September 2017.*

▲ *A group photo taken at the TEC meeting in Oct 2017. From left to right: Dr Victor TANG, Dr Bobby SHUM, Dr Jason SO, Professor KHOO Ui Soon, Professor HO Pak Leung, Dr Michael CHAN, Professor Annie CHEUNG, Dr Liz YUEN, Dr Anthony SHEK, Professor Philip BEH, Dr MAK Siu Ming.*

Fellows' Laurels

Professor Malik PEIRIS elected as a foreign associate of the National Academy of Sciences (NAS) of the United States of America

On 2 May 2017, the National Academy of Sciences (NAS) of the United States of America (US) announced Professor Malik PEIRIS, a Fellow of our College, as one of their newly elected foreign associates. Members are elected to the NAS in recognition of their distinguished and continuing achievements in original research. Membership is an indication of excellence in science and is considered one of the highest honours that a scientist can receive. NAS membership is achieved by election, and only Academy members may submit formal nominations, which are followed by a vetting process that results in a final ballot at the annual meeting of the NAS in April each year. A maximum of 84 members may be elected annually. Members must be US citizens; non-citizens are elected as foreign associates, with a maximum of 21 elected annually. Currently, the NAS membership totals approximately 2,290 members and nearly 460 foreign associates, of whom approximately 200 have received Nobel prizes. Professor Peiris is currently Chair Professor of Virology of School of Public Health, Li Ka Shing Faculty of Medicine, the University of Hong Kong. Congratulations to Professor Peiris!

THE HONG KONG COLLEGE OF PATHOLOGISTS:

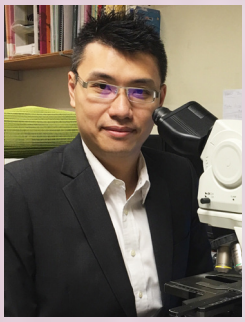
TOPICAL UPDATE

Volume 12, Issue 2 August 2017

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

Editorial note: *Gastrointestinal stromal tumor is the commonest mesenchymal tumor in the digestive system. It is a genetically heterogeneous disease with various mutations apart from classical activation mutations in KIT and PDGFRA genes. In the topical update, Dr. Anthony Chan provided an overview of molecular alterations of gastrointestinal stromal tumor with emphasis on their prognostic and therapeutic significance. We welcome any feedback or suggestions. Please direct them to Dr. Anthony Chan (e-mail: awh_chan@cuhk.edu.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.*

Molecular alterations of gastrointestinal stromal tumor - Prognostic and therapeutic implications



Dr. Anthony W.H. Chan
Clinical Associate Professor
Department of Anatomical and Cellular Pathology,
Prince of Wales Hospital,
The Chinese University of Hong Kong

The gist of GIST

Gastrointestinal stromal tumor (GIST) is a rare tumor with the annual incidence rate of 10-15/1,000,000, but it is the commonest mesenchymal tumor in the digestive system. It affects both sexes equally and presents at any age from children to elderly with the median age of mid 60s. Stomach (55.6%) is the most frequent primary tumor site followed by small intestine (31.8%), large intestine (6.0%) and esophagus (0.7%). Other uncommon primary sites, such as omentum, mesentery and liver, accounts for 5.5% of all GISTs.[1] Important milestones of GIST in diagnostic, prognostic and therapeutic aspects are briefly summarized in this section.

In the past, GIST was regarded as leiomyoma, leiomyoblastoma or leiomyosarcoma before the era of wide availability of immunohistochemistry. In 1983, Mazur and Clark first applied the term "stromal tumor" to describe a group of gastric mesenchymal tumor lacking ultrastructural features of smooth muscle or schwann cells.[2] In 1989, a short-lived term, gastrointestinal autonomic nerve tumor (GANT), was used to describe a small subset of GIST featured by small intestinal location, epithelioid appearance and focal immunoreactivity towards neural markers (S100, neurofilament and synaptophysin).[3] In 1995, CD34 was found to be the first useful diagnostic immunohistochemical marker to differentiate GIST from leiomyoma and schwannoma although only 60-70% of all GISTs are immunoreactive to CD34.[4] In 1998, the hallmark constitutive activation mutation of *KIT* gene and overexpression of KIT/CD117 protein in GIST were discovered by Hirota et al.[5] This finding also suggested that GIST may be originated from interstitial cells of Cajal, pacemaker cells of intestine, which express KIT and CD34. However, activation mutation of *KIT* gene and overexpression of KIT are not consistently correlated. A subset of KIT positive GISTs was found to lack *KIT* mutation and this observation led to the subsequent discovery of gain-of-function mutation of platelet-derived growth factor receptor alpha *(PDGFRA)* gene in 2003.[6,7] KIT and PDGFRA mutations are mutually exclusive. About 5-10% of GISTs, particularly those with *PDGFRA* mutation do not express KIT. In 2004, West et al. identified a novel gene, *DOG1* (discovered on GIST-1), through

GROUP	SIZE (CM)	MITOSIS (/50 HPF)
Very low risk	<2	≤5
Low risk	2-5	≤5
Intermediate risk	<5	6-10
	5-10	≤5
High risk	>5	>5
	>10	Any
	Any	>10

▲ *Table 1: NIH risk stratification for GIST [14]*

cDNA microarray, and showed DOG1 protein was highly expressed in GISTs (97.8%), including those KIT negative GISTs.[8] KIT and/or DOG1 become crucial diagnostic immunohistochemical markers for GIST. A small subgroup of GISTs with immunoreactivity of KIT/DOG1 lack neither *KIT* or *PDGFRA* mutation was first designated as wild-type GISTs in the same year.[9] Wild-type GISTs are later shown to be a heterogeneous group with various mutations.[10-13]

Prognosis of patients with GIST is shown to be correlated with tumor size and mitosis. The first consensus risk stratification was proposed by investigators in National Institutes of Health (NIH) in 2002 (Table 1).[14] Anatomical

GROUP	SIZE (CM)	MITOSIS (/50 HPF)	STOMACH	DUODENUM	JEJUNUM /ILEUM	RECTUM
1	≤2	≤5	None	None	None	None
2	>2-5	≤5	Very low	Low	Low	Low
3a	>5-10	≤5	Low	Moderate	-	-
3b	>10	≤5	Moderate	High	High	High
4	≤2	>5	None	High	-	High
5	>2-5	>5	Moderate	High	High	High
6a	>5-10	>5	High	High	-	-
6b	>10	>5	High	High	High	High

▲ *Table 2: AFIP risk stratification for GIST [15]*

GROUP	SIZE (CM)	MITOSIS (/50 HPF)	PRIMARY SITE
Very low risk	≤2	≤5	Any
Low risk	>2-5	≤5	Any
Intermediate	>2-5	>5	Gastric
Risk	≤5	6-10	Any
	>5-10	≤5	Gastric
High risk	>5	>5	Any
	>10	Any	Any
	Any	>10	Any
	Any	Any	Tumor rupture
	>2-5	>5	Non-gastric
	>5-10	≤5	Non-gastric

▲ *Table 3: Modified NIH risk stratification for GIST [16]*

GROUP	SIZE (CM)	N	M	MITOSIS (/50 HPF)
IA	≤5	0	0	≤5
IB	>5-10	0	0	≤5
II	≤5	0	0	>5
	>10	0	0	≤5
IIIA	>5-10	0	0	>5
IIIB	>10	0	0	>5
IV	Any	1	0	Any
	Any	Any	1	Any

▲ *Table 4: AJCC staging system for gastric and omental GIST*

GROUP	SIZE (CM)	N	M	MITOSIS (/50 HPF)
IA	≤5	0	0	≤5
I	≤5	0	0	≤5
II	>5-10	0	0	≤5
IIIA	≤2	0	0	>5
	>10	0	0	≤5
IIIB	>2	0	0	>5
IV	Any	1	0	Any
	Any	Any	1	Any

▲ *Table 5: AJCC staging system for small/large bowel, esophageal, mesenteric and peritoneal GIST*

Study	Region	n	KIT exon				PDGFRA exon			Wild type
			9	11	13	17	12	14	18	
Wozniak 2012(24)	Poland	427	7.3%	61.1%	0.5%	0.5%	0.2%	0.7%	11.9%	17.8%
Wozniak 2014 (28)	Europe	1056	7.4%	61.4%	1.8%	0.6%	0.9%	0.3%	12.8%	14.9%
Künstlinger 2013 (25)	Germany	1366	9.2%	59.3%	1.8%	0.8%	1.8%	0.6%	13.8%	12.7%
Wang 2014 (27)	China	275	10.9%	77.1%	1.1%	0.0%	1.1%	0.0%	3.6%	6.2%
Rossi 2015 (29)	Italy	451	7.1%	56.1%	0.9%	0.7%	2.2%	1.6%	17.3%	14.2%
ACOSOG Z9001 (26)		507	6.9%	67.3%	1.8%	0.2%	NA	NA	NA	12.8%
CALGB 150105 (23)		378	8.2%	72.8%	0.8%	1.1%	0.0%	0.0%	1.6%	15.3%
EORTC 62005 (22)		377	15.4%	65.8%	1.6%	0.8%	0.8%	0.0%	1.9%	13.8%

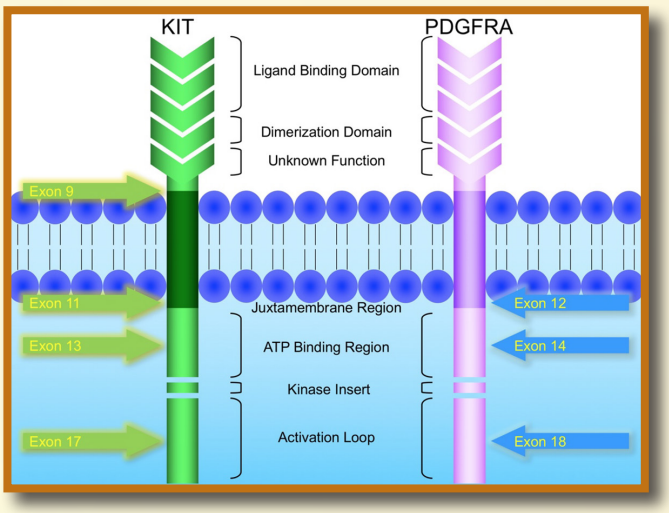
▲ *Table 6: Mutational landscape of GIST*

location of GIST is also an important prognostic factor and firstly integrated to the Armed Forces Institute of Pathology system in 2006 (Table 2)[15]. Gastric GIST behaves more indolent than small and large bowel GIST with similar size and mitosis. Tumor rupture is an additional prognosticator for GIST patients and incorporated into the modified NIH system in 2008 (Table 3).[16] Finally, the most widely adopted tumor staging system, American Joint Committee on Cancer (AJCC), include GIST risk stratification composed of tumor size, mitosis, anatomical location, nodal and distant metastases in the 7th edition in 2010, which remains unchanged in the recently released 8th edition (Table 4 and 5).

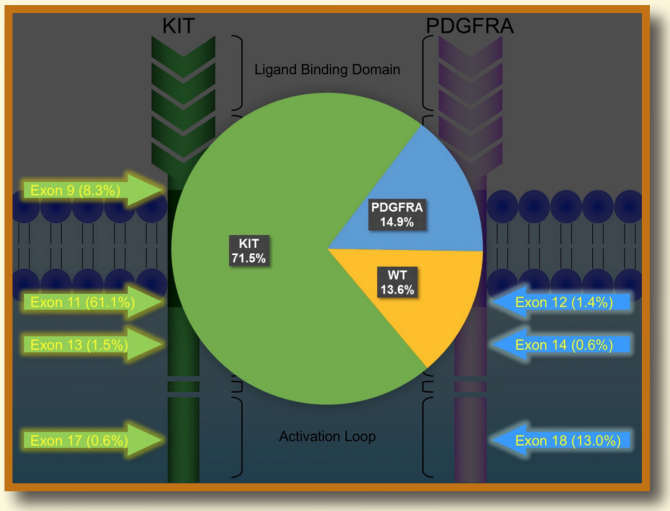
Surgical resection remains the mainstay of curative therapy for GIST but a substantial portion of GIST patients present in advanced stage beyond surgical intervention. Imatinib, a multi-targeted tyrosine kinase inhibitor specific for c-abl, c-kit and PDGFR, was first used in a patient with metastatic GIST in 2001.[17] The dramatic clinical response from this patient and the subsequent successful phase II clinical trial in 2002 secured the first-line role of imatinib for patients with inoperable GIST and pioneered molecular targeted therapy for sarcoma.[18] Primary and acquired resistance to imatinib among GIST patients led to development of newer targeted agents. Two hallmark phase III randomized controlled trials on sunitinib (NCT00075218) and regorafenib (NCT01271712) for GIST were completed in 2006 and 2013, respectively.[19, 20] Sunitinib and regorafenib are indicated for patients with advanced GIST resistant or intolerant to imatinib.

Mutational landscape of GIST

KIT and *PDGFRA* mutations are major driver mutations in GIST tumorigenesis. Both genes encode type III receptor tyrosine kinases with similar structures: extracellular ligand binding domain and dimerization domain, a transmembrane sequence, a juxtamembrane domain and intracellular kinase domain (Figure 1). Binding of corresponding ligands, stem cell factor and PDGFA, to c-kit and PDGFRA receptor, respectively, dimerizes and activates receptor tyrosine kinases. In GIST, activation mutations in *KIT* and *PDGFRA* lead to uncontrolled ligand-independent receptor activation. Mutation hotspots of *KIT* gene are located at exons 9, 11, 13 and 17, whereas those of PDGFRA gene are situated at exons 12, 14 and 18. Mutation of extracellular domain of *KIT* encoded by exon 9 facilitate receptor dimerization. Mutations in the juxtamembrane domain, which is encoded by exon 11 of *KIT* and exon 12 of *PDGFRA*, allow dimerization of receptor without binding of ligands. Mutations of ATP binding region of kinase domain (encoded by exon 13 of *KIT* and exon 14 of *PDGFRA*) enhance kinase activity, while mutations



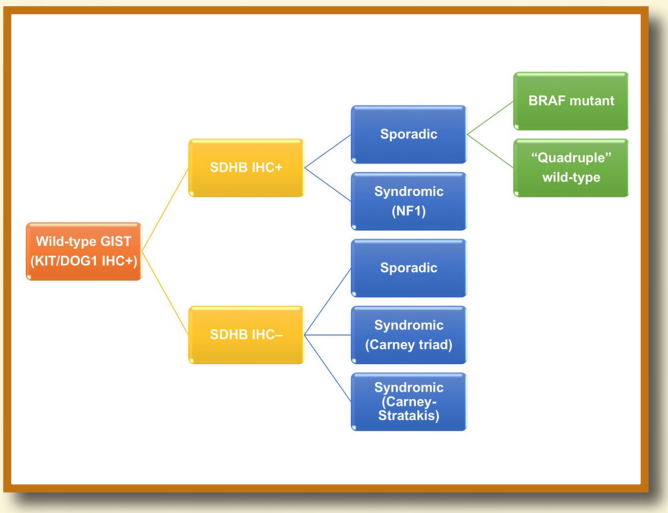
▲ ***Figure 1: Schematic diagram of the structures of KIT and PDGFRA receptor tyrosine kinases***



▲ ***Figure 2: Mutational landscape of GIST***

of activation loop (encoded by exon 17 of *KIT* and exon 18 of *PDGFRA*) promote active conformation of kinase.[21] Table 6 and Figure 2 summarize the mutational landscape of GIST based on the data from population-based studies and clinical trials.[22-29] Frequencies of *PDGFRA* mutations are significantly lower among patients in clinical trials (mean 1.7%) than those in population-based studies (mean 14.9%) because GIST patients with *PDGFRA* mutations are associated with better prognosis and earlier stage and hence do not require systemic therapy.[9, 22, 23, 29]

KIT mutation accounts for 71.5% (64.8-89.1%) of mutations in GISTs.[24, 25, 27-29] Exon 11 mutation is the commonest mutation (61.1%, range: 56.1-77.1%). Deletion, substitution and duplication contribute to 23-28%, 2-20% and 2-7%, respectively. Deletion in exon 11 is associated with younger age, larger tumor size, higher mitotic count and poor prognosis, whereas duplication is associated with female and stomach predilection and better prognosis. Exon 9 mutation is found in 7.1-10.9% of GISTs, particularly in those arising from small and large intestine, and associated with poor prognosis.



▲ ***Figure 3: Classification of wild-type GIST***

Exon 13 and exon 17 are rare mutation hotspots (<1-2%) in GISTs, which are almost exclusively spindle in morphology and more frequently developed in small intestine. GISTs with exon 13 and 17 mutants are associated good and intermediate prognosis, respectively.

PDGFRA mutation accounts for 14.9% (4.7-21.1%) of mutations in GISTs.[24, 25, 27-29] About 30-40% of GISTs without immunoreactivity of KIT/CD117 harbour *PDGFRA* mutation. GISTs with PDGFRA mutation generally show predilection to gastric location (>90%) and epithelioid/mixed morphology, and favourable prognosis (except non-D842V exon 18 mutation).

Wild-type GIST, which express immunoreactivity of KIT/DOG1 but lack neither *KIT* or *PDGFRA* mutation, contributes to 13-18% of adult GISTs and 85% of pediatric GIST.[10-12] As previously mentioned, it is a genetically heterogeneous group (Figure 3). Wild-type GIST can be further stratified by using succinate dehydrogenase B (SDHB) immunohistochemistry and familial syndromes. On one hand, SDHB deficient wild-type GISTs accounts for about 5% of all GISTs, and can be sporadic or related to Carney triad and Carney-Stratakis syndrome. Carney triad is a constellation of GIST, paraganglioma and pulmonary chondroma with undetermined germline mutation, whereas Carney-Stratakis syndrome is an autosomal dominant disease with dyad of GIST and paraganglioma, and germline mutations in *SDHB*, *SDHC* or *SDHD* genes.[30] SDHB deficient wild-type GISTs are featured by female predominance (except for Carney-Stratakis syndrome), exclusive location in stomach, multifocality, epithelioid/mixed morphology, unpredictable clinical outcome by histology, indolent clinical course despite frequent nodal metastasis, and mutation id SDH subunits (except for Carney triad). On the other hand, SDHB proficient wild-type GISTs make up 10.5% of all GISTs, and are either sporadic (9%) or syndromic (1.5%). Syndromic SDHB proficient wild-type GISTs are associated with neurofibromatosis type 1, absence of sex/age predilection, small intestine in location, multifocality, spindle morphology, and favorable prognosis. Sporadic SDHB proficient wild-type GISTs can be further classified according to *BRAF* mutation. Sporadic SDHB proficient wild-type GISTs with *BRAF* mutation usually occur in 6th decade of age and small intestine with spindle morphology. Prognosis of this subgroup is inconclusive.[10, 29, 31, 32] Sporadic SDHB proficient wild-type GISTs without *BRAF* mutation are also known as quadruple wild-type GISTs without any mutation in *KIT*, *PDGFRA*, *SDH* and genes in RAS pathway *(BRAF/NF1)*.[12, 13] They represent the commonest subgroup (7%) of wild-type GISTs and a genetically heterogeneous subgroup harboring *ETV6-NTRK3* translocation, FGFR1-TACC1 translocation, mutation of *MEN1* and *MAX*, and overexpression of *COL22A1* and *CALCRL*.[12, 29, 33, 34] Due to complex genetic heterogeneity, clinicopathological features of this subgroup have not been well characterized.

Clinical implications of mutations in GIST

Different mutations in GIST have their own characteristic prognostic and therapeutic implications. Prognostic significance of individual mutations have been described by various investigators and briefly mentioned in the previous section. Rossi et al. recently systemically analyzed the prognostic impact of mutations among 451 patients with primary localized treatment-naive GISTs.[29] By multivariable Cox regression, mutational status was an independent prognosticator in addition to patient's age, tumor location, tumor size and mitotic count. Three molecular risk groups with prognostic significance were identified: Group 1 with the most favorable outcome is composed of mutations in KIT exon 13, PDGFRA exon 12 and BRAF; Group 2 with the intermediate outcome (hazard ratio 3.06) consists of *KIT/PDGFRA/BRAF* triple negative, and mutations in *KIT* exon 17, *PDGFA* exon 14 and 18 (D842V); and Group 3 with the most unfavorable outcome comprises mutations in *KIT* exon 9 and 11, and *PDGFRA* exon 18 (non-D842V).

Clinical response toward imatinib among GIST patients is closely related to tumor genotype. In a phase III clinical trial (SWOG S0033/CALGB 150105), the investigators demonstrated that patients with *KIT* exon 11 mutation (complete response [CR]/partial response [PR] 71.7%) had better response to imatinib than those with *KIT* exon 9 mutation (CR/PR 44.4%) and wild-type *KIT* (CR/PR 44.6%).[23] They also showed that doubling the dose of imatinib (from 400 mg to 800 mg) improved response rates for patients with exon 9-mutant tumors (CR/PR 17% vs. 67%). Double dose of imatinib did not offer any better response rate among patients with exon 11 mutant or wild-type *KIT*. A subsequent meta-analysis of 1,640 patients with advanced GIST receiving

imatinib confirmed that double dose of imatinib improved progression-free survival and objective response rate, but not overall survival, among patients with *KIT* exon 9-mutant GIST.[35] *PDGFA* exon 18 (D842V) mutation and *KIT/PDGFRA* wild-type are responsible for primary resistance to imatinib.[36] Among patients with advanced GIST receiving imatinib, a substantial proportion of initial responders will develop acquired resistance. Secondary mutations in exon 11 (L576P and V559A), exon 13 (V654A), exon 14 (T670I), exon 17 and exon 18 (A829P) of *KIT*, and exon 18 of *PDGFRA* are related to acquired resistance to imatinib.[36]

Clinical response to sunitinib, the second line targeted therapy after imatinib failure, is also considerably affected by primary and acquired mutations of *KIT* Patients with primary KIT exon 9 mutation or wild-type *KIT* had better overall and progression-free survival than those with *KIT* exon 11 mutation, whereas patients with acquired KIT exons 13 or 14 mutations had better outcome than those with *KIT* exon 17 or 18 mutations.[37] Similarly, clinical response to regorafenib, the third line therapy after imatinib and sunitinib failure, is significantly influenced by tumor genotype. Regorafenib provided better clinical outcome among patients with primary KIT exon 11 mutation and SDHB deficient GIST,[38] as well as those with secondary mutation of *KIT* exon 17, which are resistant to both imatinib and sunitinib.[39]

Summary

GIST is a genetically heterogeneous tumor. Genotypes and phenotypes are closely interrelated. Specific mutations have their characteristic clinicopathological features, prognostication and therapeutic implications. Genetic analyses *KIT* and *PDGFRA* are highly recommended especially among patients with advanced diseases undergoing targeted therapy. Wild-type GISTs are recommended to be further analysed by SDHB immunohistochemistry and *BRAF* mutation test.

References

1. Soreide K, Sandvik OM, Soreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. Cancer Epidemiol. 2016;40:39-46.
2. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol. 1983;7(6):507-19.
3. Herrera GA, Cerezo L, Jones JE, Sack J, Grizzle WE, Pollack WJ, et al. Gastrointestinal autonomic nerve tumors. 'Plexosarcomas'. Arch Pathol Lab Med. 1989;113(8):846-53.
4. Miettinen M, Virolainen M, Maarit Sarlomo R. Gastrointestinal stromal tumors--value of CD34 antigen in their identification and separation from true leiomyomas and schwannomas. Am J Surg Pathol. 1995;19(2):207-16.
5. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279(5350):577-80.
6. Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003;299(5607):708-10.
7. Hirota S, Ohashi A, Nishida T, Isozaki K, Kinoshita K, Shinomura Y, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology. 2003;125(3):660-7.
8. West RB, Corless CL, Chen X, Rubin BP, Subramanian S, Montgomery K, et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. Am J Pathol. 2004;165(1):107-13.
9. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol. 2004;22(18):3813-25.
10. Agaram NP, Wong GC, Guo T, Maki RG, Singer S, Dematteo RP, et al. Novel V600E BRAF mutations in imatinib-naive and imatinib-resistant gastrointestinal stromal tumors. Genes Chromosomes Cancer. 2008;47(10):853-9.
11. Janeway KA, Kim SY, Lodish M, Nose V, Rustin P, Gaal J, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci U S A. 2011;108(1):314-8.
12. Nannini M, Astolfi A, Urbini M, Indio V, Santini D, Heinrich MC, et al. Integrated genomic study of quadruple-WT GIST (KIT/PDGFRA/SDH/RAS pathway wild-type GIST). BMC Cancer. 2014;14:685.
13. Pantaleo MA, Urbini M, Indio V, Ravegnini G, Nannini M, De Luca M, et al. Genome-Wide Analysis Identifies MEN1 and MAX Mutations and a Neuroendocrine-Like Molecular Heterogeneity in Quadruple WT GIST. Mol Cancer Res. 2017;15(5):553-62.
14. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002;33(5):459-65.
15. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23(2):70-83.
16. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008;39(10):1411-9.
17. Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med. 2001;344(14):1052-6.
18. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002;347(7):472-80.
19. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329-38.
20. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295-302.
21. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer. 2011;11(12):865-78.
22. Debiec-Rychter M, Sciot R, Le Cesne A, Schlemmer M, Hohenberger P, van Oosterom AT, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer. 2006;42(8):1093-103.
23. Heinrich MC, Owzar K, Corless CL, Hollis D, Borden EC, Fletcher CD, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol. 2008;26(33):5360-7.
24. Wozniak A, Rutkowski P, Piskorz A, Ciwoniuk M, Osuch C, Bylina E, et al. Prognostic value of KIT/PDGFRA mutations in gastrointestinal stromal tumours (GIST): Polish Clinical GIST Registry experience. Ann Oncol. 2012;23(2):353-60.
25. Kunstlinger H, Huss S, Merkelbach-Bruse S, Binot E, Kleine MA, Loeser H, et al. Gastrointestinal stromal tumors with KIT exon 9 mutations: Update on genotype-phenotype correlation and validation of a high-

resolution melting assay for mutational testing. Am J Surg Pathol. 2013;37(11):1648-59.
26. Corless CL, Ballman KV, Antonescu CR, Kolesnikova V, Maki RG, Pisters PW, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol. 2014;32(15):1563-70.
27. Wang M, Xu J, Zhao W, Tu L, Qiu W, Wang C, et al. Prognostic value of mutational characteristics in gastrointestinal stromal tumors: a single-center experience in 275 cases. Med Oncol. 2014;31(1):819.
28. Wozniak A, Rutkowski P, Schoffski P, Ray-Coquard I, Hostein I, Schildhaus HU, et al. Tumor genotype is an independent prognostic factor in primary gastrointestinal stromal tumors of gastric origin: a european multicenter analysis based on ConticaGIST. Clin Cancer Res. 2014;20(23):6105-16.
29. Rossi S, Gasparotto D, Miceli R, Toffolatti L, Gallina G, Scaramel E, et al. KIT, PDGFRA, and BRAF mutational spectrum impacts on the natural history of imatinib-naive localized GIST: a population-based study. Am J Surg Pathol. 2015;39(7):922-30.
30. Stratakis CA, Carney JA. The triad of paragangliomas, gastric stromal tumours and pulmonary chondromas (Carney triad), and the dyad of paragangliomas and gastric stromal sarcomas (Carney-Stratakis syndrome): molecular genetics and clinical implications. J Intern Med. 2009;266(1):43-52.
31. Hostein I, Faur N, Primois C, Boury F, Denard J, Emile JF, et al. BRAF mutation status in gastrointestinal stromal tumors. Am J Clin Pathol. 2010;133(1):141-8.
32. Huss S, Pasternack H, Ihle MA, Merkelbach-Bruse S, Heitkotter B, Hartmann W, et al. Clinicopathological and molecular features of a large cohort of gastrointestinal stromal tumors (GISTs) and review of the literature: BRAF mutations in KIT/PDGFRA wild-type GISTs are rare events. Hum Pathol. 2017;62:206-14.
33. Brenca M, Rossi S, Polano M, Gasparotto D, Zanatta L, Racanelli D, et al. Transcriptome sequencing identifies ETV6-NTRK3 as a gene fusion involved in GIST. J Pathol. 2016;238(4):543-9.
34. Shi E, Chmielecki J, Tang CM, Wang K, Heinrich MC, Kang G, et al. FGFR1 and NTRK3 actionable alterations in "Wild-Type" gastrointestinal stromal tumors. J Transl Med. 2016;14(1):339.
35. Gastrointestinal Stromal Tumor Meta-Analysis G. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol. 2010;28(7):1247-53.
36. Sankhala KK. Clinical development landscape in GIST: from novel agents that target accessory pathways to revisiting non-targeted therapies. Expert Opin Investig Drugs. 2017;26(4):427-43.
37. Heinrich MC, Maki RG, Corless CL, Antonescu CR, Harlow A, Griffith D, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol. 2008;26(33):5352-9.
38. Ben-Ami E, Barysauskas CM, von Mehren M, Heinrich MC, Corless CL, Butrynski JE, et al. Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. Ann Oncol. 2016;27(9):1794-9.
39. Yeh CN, Chen MH, Chen YY, Yang CY, Yen CC, Tzen CY, et al. A phase II trial of regorafenib in patients with metastatic and/or a unresectable gastrointestinal stromal tumor harboring secondary mutations of exon 17. Oncotarget. 2017;8(27):44121-30.

Announcement from the Education Committee (Sep 2017)

1. CME/CPD ANNUAL RETURN 2017

To align our practice to the regulations laid down by the Hong Kong Academy of Medicine, this announcement serves to remind Fellows the Education Committee will call for CME/CPD annual return in early October as in last year. The deadline of submission will be 5th January 2018.

Nil return is not required in the first and second cycle years of the 3-year CME/CPD cycle. A minimum of 15 CME/CPD points is recommended to be achieved each year. Fellows can submit CME/CPD annual returns if there are CME/CPD activities to update or report. The CME/CPD Annual Return Form can be downloaded from the "Downloads" area of the College webpage (http://www.hkcpath.org/).

2. CME/CPD PROFILE

Please be reminded the Education Committee will no longer include individual Fellow's personal CME/CPD profile in the call-for-annual return notice. Fellows are required to login to the iCMECPD website (http://www.icmecpd.hk/) to check their own CME/CPD records.

3. "ATTENDANCE RECORD FOR INDIVIDUAL FELLOW"

To avoid the last minute rush, Fellows are encouraged to make use of the "Attendance Record for Individual Fellow" to report their CME/CPD activities (e.g. Self Study and Publications) to the Education Committee soon after completion of the CME/CPD activities. The forms can be found at http://www.hkcpath.org/resources/downloads.

Announcement from the Training and Examinations Committee

CONGRATULATIONS!!

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

CHUNG Ivy Ah-Yu
(Fellowship Assessment – Anatomical Pathology)

LAM Winwhole Larry Ruey Si
(Fellowship Assessment – Anatomical Pathology)

LEE Wai Tung
(Fellowship Assessment – Anatomical Pathology)

SHEA Ka Ho
(Fellowship Assessment – Anatomical Pathology)

SHUM Rocky
(Fellowship Assessment – Clinical Microbiology & Infection)

YUK Man Ting
(Fellowship Assessment – Clinical Microbiology & Infection)

CHAN Chun Ngai
(Fellowship Assessment – Haematology)

CHEUNG Sin
(Fellowship Assessment – Haematology)

CHAN Wing Chai Raymond
(Membership Examination – Anatomical Pathology)

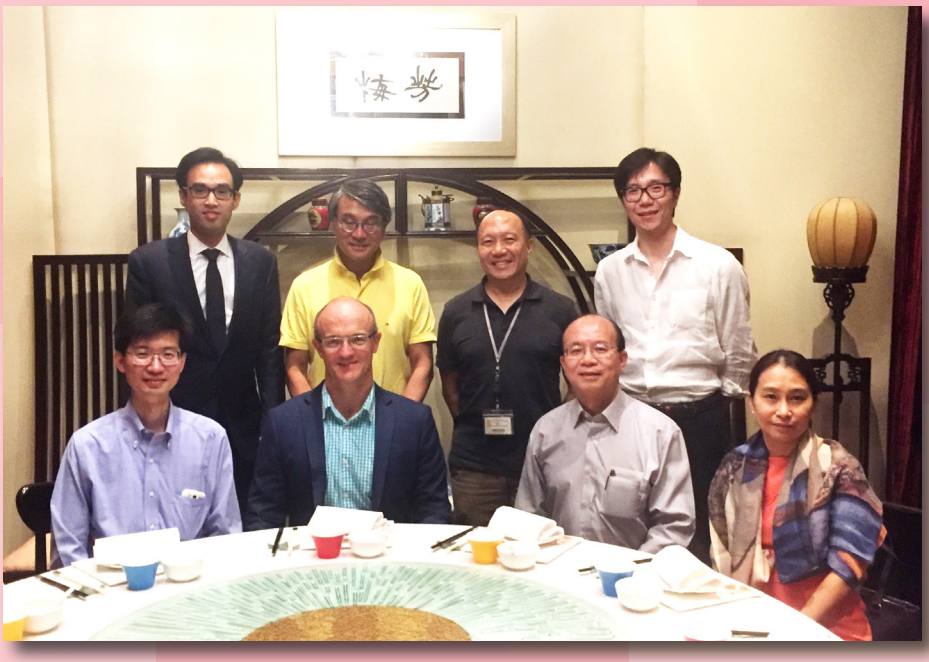
CHENG Shui Ying
(Membership Examination – Anatomical Pathology)

KAM Lok Sang
(Membership Examination – Anatomical Pathology)

LIU Kwan Leung
(Membership Examination – Anatomical Pathology)

LO Hui Yin
(Membership Examination – Anatomical Pathology)

LOK Johann
(Membership Examination – Anatomical Pathology)



▲ ***Examiners in Haematology:*** *Front row (left to right): Dr Jason SO (Chief Examiner), Dr Matthew WRIGHT (External Examiner), Dr Raymond CHU, Prof. Margaret NG*
Back row (left to right): Dr Alvin IP, Dr WONG Kit Fai, Dr Clarence LAM, Dr Rock LEUNG.

▶ ***Examiners in Anatomical Pathology:***
Front row (left to right): Dr YUEN Wah Fun, Prof. KHOO Ui Soon (Chief Examiner), Dr Martin Paul Alistair YOUNG (External Examiner), Dr LAU Lin Kiu.
Back row (left to right): Dr IP Pun Ching Philip, Dr CHAN Wai Kong, Prof. TO Ka Fai, Dr LAM Wing Yin.

▲ ***Examiners in Anatomical Pathology:*** *Front row (left to right): Dr LEUNG Chung Ying, Prof. CHEUNG Nga Yin Annie, Dr Martin Paul Alistair YOUNG (External Examiner), Prof. KHOO Ui Soon (Chief Examiner), Dr LEE Kam Cheong. Back row (left to right): Dr LUI Yun Hoi, Dr NG Wai Fu, Dr IP Pun Ching Philip, Dr LAM Wing Yin.*

Featured article:

Pathologists bid farewell to historical building

Message from Professor Annie Cheung

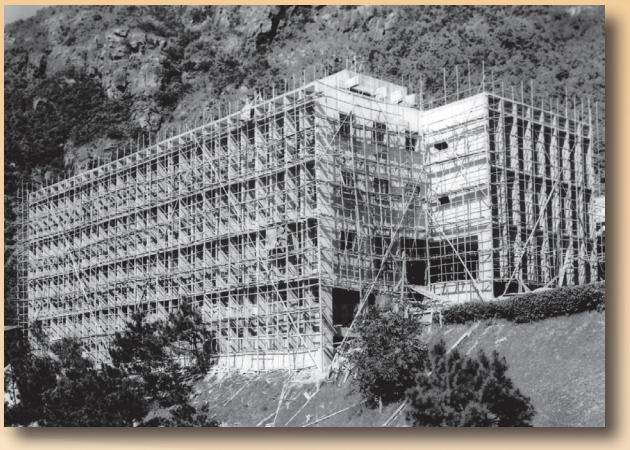
The University Pathology Building (UPB) will be decommissioned in 2018 as part of the Queen Mary Hospital (QMH) redevelopment plan. Since its establishment, UPB has played important role in the undergraduate and postgraduate education of pathology in Hong Kong as well as contributing to breakthrough in research and advancement of clinical services.

Besides lectures and practical classes for pathology teaching for medical students, postgraduate courses for medical and related professions are also held in UPB. UPB is also the venue for the annual College examinations. In recent years, educational workshop for the public, particularly high school students, are often conducted in UPB as activities to publicize the International Pathology Day.

To cherish fond memories of UPB and to celebrate its historical importance, the University of Hong Kong Departments of Microbiology and Pathology jointly organized a "Farewell to UPB" on October 21, 2017. I am very happy to report that many alumni, colleagues and old friends came back for this very special occasion to share our memories.

UPB has become my second home. As a medical student and a University staff, I have been learning and working in UPB for more than 30 years! Although UPB will soon finish its mission, there is no doubt in my mind that the memory will be treasured by many of us.

.



▲ *University Pathology Building under construction in 1950s*

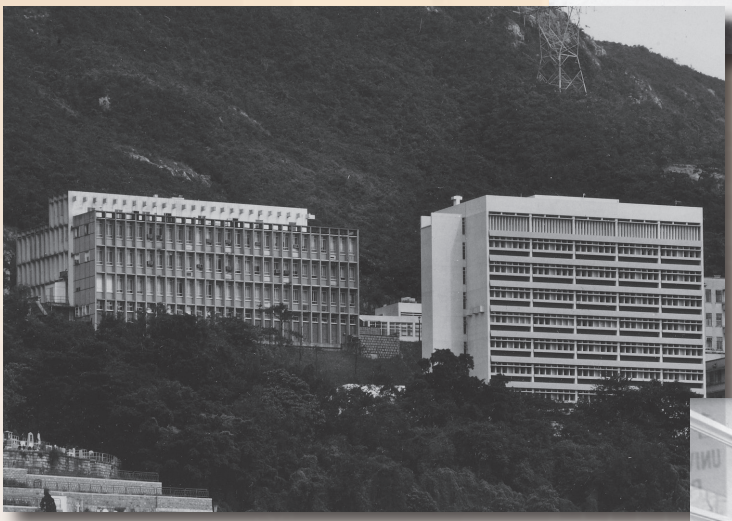
▲ *Prof. PC Hou (left) with guests on the roof of University Pathology Building*

▲ *Prof. PC Hou (first right of first row), Prof Lin Ma (first left of second row) and colleagues of Pathology before the University Pathology Building on 22nd January, 1959*

Message from Professor Irene Ng

The University Pathology Building, which we fondly call UPB, has a history of almost 60 years. It is a very special building to many of us and is a place full of history and memories. We say it is the memories and people that make a work place, not the things in it or the structure itself. I can vividly remember my former respectable professors, seniors and colleagues. I had studied here as a medical student and have been working in the building soon after I graduated. In this building, we have a wealth of knowledge and fond memories which we will always treasure. Yet soon we are to leave this treasured building behind. We hope our fond memories in and for the building will be captured and passed down.

▲ *Prof. James Gibson (centre of first row) and colleagues, including Dr Hsiangju Lin (first left of first row) and Dr WC Chan (second left of first row), before the Building*



▲ *University Pathology Building and Clinical Pathology Building in 1960s-70s*

▶ *Prof. James Gibson (third left of first row) and colleagues, including Prof. F Ho (fourth from right), Prof. PC Wu (first left of first row), Dr C Hsu (second from right), Dr WL Ng (first left of second row) and Dr KF So (third left of second row), at the entrance of the Building after the restructuring in 1970s.*

Message from Professor Patrick Woo

The University Pathology Building and Clinical Pathology Building represent an ocean of memories. I learned my microbiology and pathology in UPB/CPB 30 years ago as a medical student. All my microbiology teachers have retired or left the university, but many of my pathology teachers have become my colleagues. The haunted, slow, inefficient elevators, the extra-crowded laboratories, the amplicons that have contaminated all the PCR reactions, all the people whom I have quarrelled with, will become sweet memories. Dear UPB/CBP, we are moving and are going to meet new friends at Block T. Please bless us in the days and years to come.

▲ *Left to right: Prof. Annie Cheung, Ms Bella Ho, Prof. Irene Ng, Dr Maria Wong, Dr Alvin Pang, Prof. Rosie Young, Prof. KY Yuen & Dr Florence Cheung*

▲ *Group photo of fellows and guests*

▲ *Fellows at the event*

▼ *Happy reunion of anatomical pathologists*

▲ *Happy reunion of microbiologists*

▲ *University Pathology Buildng and Clinical Pathology Building*

▲ *Prof. MH Ng*

◀ *Dr Laurence Hou*

▼ *Dr Lily Ma*

▲ *Dr Raymond Yung*

▲ *Left to right: Prof. Annie Cheung, Prof. Gabriel Leung, Dean of LKS Faculty of Medicine, HKU, Prof. Irene Ng & Prof. US Khoo*

▲ *Left to right: Dr Raymond Yung, Prof. Irene Ng & Dr CC Luk, HCE, QMH*

Programme of the 26th Annual General Meeting

25 November 2017 (Saturday)

Pao Yue Kong Auditorium, Ground Floor,
HKAM Jockey Club Building, 99 Wong Chuk Hang Road,
Aberdeen, Hong Kong.

1:00 p.m. – 5:00 p.m.	The 13th Trainee Presentation Session
5:00 p.m. – 5:30 p.m.	The 26th Annual General Meeting
5:30 p.m. – 6:00 p.m.	Reception
6:00 p.m. – 6:50 p.m.	Conferment Ceremony Admission of New Fellows and Members and Presentation of Fellowship and Membership Certificates Conclusion of Conferment Ceremony
6:50 p.m. – 7:00 p.m.	Group Photo of Stage Party
7:00 p.m. – 8:00 p.m.	The 26th T. B. Teoh Foundation Lecture: "From Prenatal to Cancer Assessments: the Power of Precision Diagnostics" Professor CHIU Wai Kwun, Rossa Choh-Ming Li Professor of Chemical Pathology Assistant Dean (Research) The Faculty of Medicine The Chinese University of Hong Kong
8:00 p.m. – 10:00 p.m.	Chinese Banquet Dinner