出國報告（出國類別：參加國際會議）

第三屆上海表觀遺傳學在發育與疾病國際研討會 會議心得報告

服務機關：國立中正大學 生命科學系

姓名職稱：陳永恩 助理教授

派赴國家：中國 大陸

出國期間：中華民國 101 年 4 月 19 日至 4 月 24 日

報告日期：中華民國 101 年 5 月

摘要

自 James Watson 和 Francis Crick 發現 DNA 三度空間結構後，人類對基因的了解有了進一步的了解。但對於基因如何調控，還不是非常清楚。過去 20 年來，分子生物學家，發現了 DNA(ATCG)四種核核苷酸以外的調控。透過表觀遺傳(epigenetics)的改變，在不影響基因序列之情況下，因爲基因甲基化(DNA methylation)及組織蛋白(histone)的修飾，卻可改變基因的表達。2012 年 4 月 19-22 日於上海復旦大學舉行的，「第三屆上海表觀遺傳學在發育與疾病國際研討會」，在會議中除了發表壁報論文外，最重要是參與 46 位國際級講員之成果報告及討論表觀遺傳在細胞發育及人類疾病之關係。在人類疾病上，除了討論表觀遺傳與癌症的關係外，也特別討論表觀遺傳與精神情緒疾病/行爲偏差的關係。

目次

一、參加目的

表觀遺傳學(epigenetics)的改變包括基因甲基化(DNA methylation)及組織蛋白(histone)的修飾，在基因序列沒有改變之下，卻可改變基因的表達。在人類的基因體中，基因甲基化常發生在基因的起動子(promoter)之 CpG 島上，而調控基因的表現。過去十年來的研究發現異常表基因變異(epigenetic changes)會導致癌症的發生，而近年來的研究更發現表基因變異與細胞發育及其相關疾病以及人類行爲變異都有關係。本次所參加的「第三屆上海表觀遺傳學在發育與疾病國際研討會」，由上海交通大學及復旦大學共同主辦，於 2012 年 4 月 19-22 日，在復旦大學醫學院舉行，目的是討論表觀遺傳學在發育與人類疾病的最近研究，本人亦在會議中發表壁報論文。

二、會議過程（詳細會議議程請參附錄）

第 (4/19)
中午到達上海虹後，到復旦大學醫學院，完成報到程序。

第二天 (4/20)
8:45am - 12:00pm 表觀遺傳的化學及參與者
1:30pm - 5:10pm 表觀基因體在系統生物學中的作用
5:10pm - 6:40pm 壁報論文討論

第三天 (4/21)
8:20am – 12:00pm 癌症表觀遺傳
1:30pm – 5:10pm 表觀遺傳在其他疾病的角色
5:10pm - 6:40pm 壁報論文討論

第四天 (4/22)
8:20am - 12:00pm 表觀遺傳在生物系統的角色(1)
1:30pm - 4:00pm 表觀遺傳在生物系統的角色(2)

第五天 (4/23)
早上 參訪上海交通大學醫學院附屬仁濟醫院 討論研究合作
下午 到達香港，參訪香港中文大學醫學院 討論研究合作

第六天 (4/24)
早上抵達台灣

三、會議心得

本次會議由上海交通大學及復旦大學聯合主辦，相關會議已經是第三屆。大會共邀請了從美國(7 位)、日本(7 位)、新加坡(7 位)、中國大陸(7 位)、韓國(4 位)、德國(2 位)、澳洲(2 位)、台灣(2 位)、及荷蘭、瑞士、英國、以色列、西班牙、澳洲、印度、加拿大、香港共 46 位國際級講員。而與會者大約有 200 人。總體來說這次會議討論了表觀遺傳學的機制、在發育生物學上的角色以及和人類疾病的關係:

1．表觀遺傳的化學及參與者

本次會議針對 DNA demethylation 的機制有非常多的討論，因爲 Tet 蛋白質的發現，本次會議有許演講討論了去甲基化的機制，發現 5mC 會經由 Tet 及 BER 的作用產生－5hmC、5fC、 5caC 以達到主動去甲基化。這機制在胚胎發育的過程非常重，因此，基因甲基化的調控(epigenetic reprogramming)在細胞發育初期非常重要。而其中 Xu Guoliang 研究員的演講提到，Tet3 蛋白在受精後，會進入精子之 DNA 中，產生 5hmC，從而進行甲基化。

2．表觀基因體在系統生物學中的作用

在第二堂場演講中，主要討論表觀基因體在系統生物學中的作用。其中 UCSD 的 Ren Bing 研究員，利用 hi-C 技術發現，相同的染色體區域會相互作用，形成一個染色體的區間(compartment)。而澳洲的 Susan Clark 研究員則利用 BisChIP-Seq 技術，進一步釐清 H3K27me3 與 DNA methylation 的關係，發現不是完全彼此互斥。

3．表觀遺傳與疾病

在第三及第四堂分別討論了表觀遺傳在癌症及其他疾病(例如精神相關疾病)的關係。在癌症方面，除了討論了癌症與基因甲基化的變異有關，以及在臨床上的應用，台灣的研究員 Juan Li-Jung 研究員發現 Tet1 除了是控制 DNA demethylation 的一個重要蛋白，也可能在癌細胞中，辦演 tumor suppressor 的角色。除了癌症外，表觀遺傳中之異常甲基化現象，也發現與精神情緒疾病或行爲偏差有關。例如，日本的 Kazuya Iwamoto 發現躁鬱症的病人腦部出現異常基因甲基化。而瑞士的 Isabelle Mansuy，利用小鼠動物模式，發現長期使小鼠與母鼠分離，會使小鼠出現一些恐慌現象，此現象可以遺傳至第三代，而利用甲基化分析發現，數過基因之起動子發生異常甲基化。

4．表觀遺傳在生物系統的角色

在最後一天的會議中，各研究員討論了表觀遺傳在生物系統的角色，其中包括基因甲基化/去甲基化的機制，染色體的三度空間結構等。

5. 會議後參訪行程

會議結束後利用 4/23 日 1 天的時間，分別到上海交通大學醫學院附屬仁濟醫院及過境香港時到中文大學醫學院參訪。

上海交通大學是中國大陸的重點大學，而仁濟醫院爲其重要之教學醫院。本次參訪之實驗室爲仁濟醫院之婦癌實驗室。該實驗室爲上海重點實驗室(Key laboratory in Gynecological cancer)，實驗室之主持人張殊教授，爲本人在美國工作時一同研究卵巢癌之合作者。2008 年本人便與張教授共同發表有關卵巢癌幹細胞之論文。本次參訪主要討論如何進一步加強在卵巢癌幹細胞之研究合作。

下午到達香港後，主要行程爲參訪香港中文大學醫學院。香港中文大學醫學院位於沙田威爾斯親王醫院(Prince of Wales Hospital)，本次參訪之目的，主要是與香港中文大學消化疾病研究所(Institute of Digestive Disease)鄭詩樂博士討論胃癌之研究合作。鄭博士爲本人於胃癌研究上之長期合作者，也是長期研究癌症與在表基因之研究者。

總結:

本次會議收獲良多，從 40 多位國際級的講員中，可以很全面的了解表觀遺傳的最新研究，在各生物系統及疾病中，都辦演重要的角色。在這次會議中，有 7 位講員是來自中國大陸，可以發現，中國大陸對表觀遺傳的投資與重視。在 2008 年，國立中正大學生命科學系曾經舉辦過第一屆 cancer epigenomics meeting。期望相關單位，能補助國內大學或研究機構，能多舉辦表觀遺傳相關國際會議，以致推動表觀遺傳在台灣的研究與發展。

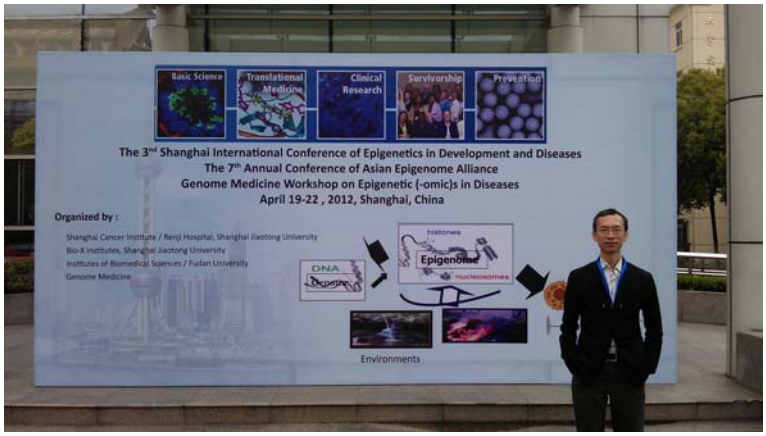
至於參訪上海交通大學與香港中文大學時，發現這兩所學校對癌症研究的重視及發展，未來希望可以加強與他們在表基因及癌症研究的合作，而其中也落實邀請香港中文大學鄭詩樂博士明年來台灣演講，進一步加強台港兩地在研究上之交流。

四、回單位後報告情形

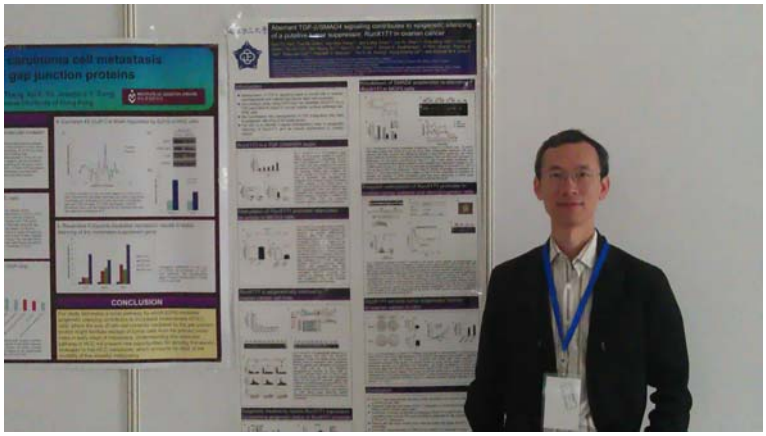
於民國 101 年 5 月 11 日在生命科學系專題討論課程中報告此次會議新知與心得。

五、附錄

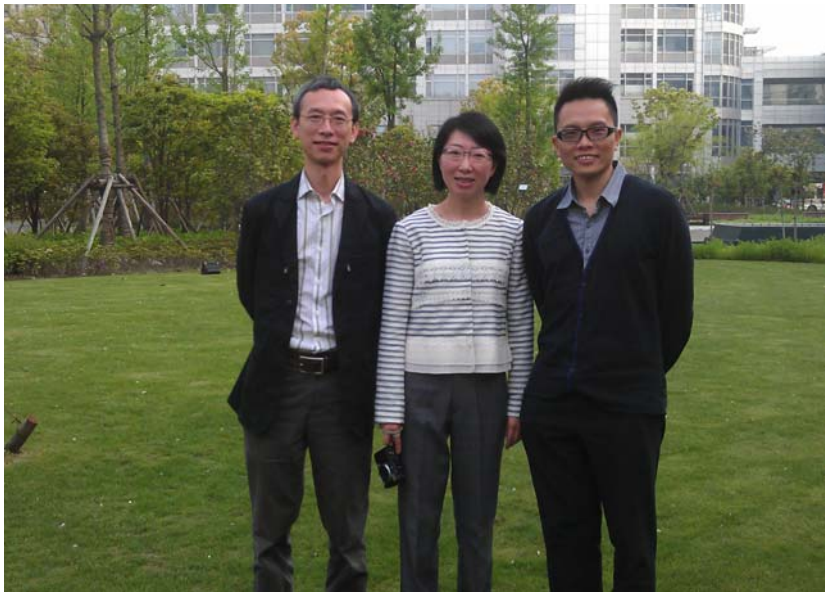
圖一：會議場地：復旦大學 醫學院



圖二：會場門口



圖三:在會場發表壁報論文



圖四:與上海仁濟醫院婦產科張殊教授(中)及香港中文大學鄭詩樂博士(右)合照

發表之論文摘要

Aberrant TGF-beta/SMAD4 signaling contributes to epigenetic silencing of a putative tumor suppressor, *RunX1T1* in ovarian cancer

Kun-Tu Yeh[1,12,13]*, Tze-Ho Chen[2,]*, Hui-Wen Yang[3,4], Jian-Liang Chou[3,4], Lin-Yu Chen[3,4], Chia-Ming Yeh[3,4], Yu-Hsin Chen[3], Ru-Inn Lin[6], Her-Young Su[7,8], Gary C.-W. Chen[3,4], Daniel E. Deatherage[9], Yi-Wen Huang[9], Pearlly S. Yan[9], Huey-Jen Lin[9,10], Kenneth P. Nephew[11], Tim H.-M. Huang[9], Hung-Cheng Lai[7,8] and Michael W.Y. Chan[3,5 ‡]

[1]Department of Pathology and [2]Department of Obstetrics and Gynecology, Changhua Christian Hospital, Changhua, Taiwan, ROC

[3]Department of Life Science and [4]Institute of Molecular Biology and [5]Human Epigenomics Center, National Chung Cheng University, Min-Hsiung, Chia-Yi, Taiwan, ROC

[6]Department of Radiation Oncology, Buddist Tzu Chi General Hospital, Dalin Branch, Taiwan

[7]Graduate Institute of Medical Sciences, and [8]Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC

[9]Human Cancer Genetics Program, Department of Molecular Virology, Immunology, and Medical Genetics, Comprehensive Cancer Center; [10]Division of Medical Technology, School of Allied Medical Professions, the Ohio State University, Columbus, Ohio, USA

[11]Medical Sciences, Indiana University School of Medicine, Bloomington, IN, USA

[12]Institute of Clinical Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, ROC

[13]School of Medicine, Chung Shan Medical University, Taichung, Taiwan, ROC

[*]these authors contribute equally to this work

[‡]Correspondence author

Abstract

Aberrant TGF-beta signaling pathway may alter the expression of down-stream targets and promotes ovarian carcinogenesis. However, the mechanism of this impairment is not fully understood. Our previous study has identified *RunX1T1* as a putative SMAD4 target in an immortalized ovarian surface epithelial cell line, IOSE. In this study, we report that transcription of *RunX1T1* was confirmed to be positively regulated by SMAD4 in IOSE cells and epigenetically silenced in a panel of ovarian cancer cell lines by promoter hypermethylation and histone methylation at H3 lysine 9. SMAD4 depletion increased repressive histone modifications of *RunX1T1* promoter without affecting promoter methylation in IOSE cells. Epigenetic treatment can restore *RunX1T1* expression by reversing its epigenetic status in MCP3 ovarian cancer cells. When transiently treated with a demethylating agent, the expression of *RunX1T1* was partially restored in MCP3 cells, but gradual re-silencing through promoter re-methylation was observed after the treatment. Interestingly, SMAD4 knockdown accelerated this re-silencing process, suggesting that normal TGF-beta signaling is essential for the maintenance of *RunX1T1* expression. *In vivo* analysis confirmed that hypermethylation of *RunX1T1* was detected in 35.7% (34/95) of ovarian tumors with high clinical stages (P=0.035) and in 83% (5/6) of primary ovarian cancer-initiating cells. Additionally, concurrent methylation of *RunX1T1* and another SMAD4 target, *FBXO32* which was previously found to be hypermethylated in ovarian cancer was observed in this same sample cohort (P<0.05). Restoration of *RunX1T1* inhibited cancer cell growth. Taken together, dysregulated TGF-beta/SMAD4 signaling may lead to epigenetic silencing of a putative tumor suppressor, *RunX1T1*, during ovarian carcinogenesis.

會議議程

The 3rd Shanghai International Conference of Epigenetics in Development and Diseases.

Chairman's Address

Epigenetics concerns the signals, players and DNA sequence independent mechanisms that underpin the cross-cell–division-maintenance of transcriptional memory. Epigenetic events modified and relay the genetic information in the genome, via RNA and protein intermediates, to the phenotypes of cells, which diversify greatly in a time- and space-specific fashion. Epigenetic wellbeing is required for the correct unfolding of gene expression programs for the cell lineage specification in development of high eukaryotes. Defects in the epigenomic homeostasis and epigenetic make-up are the hallmarks of the disease, including cancer, metabolic disorders, autoimmune and neurological diseases.

In the year celebrating the 50th anniversary of the publication of DNA's double stranded structure in Nature, James Watson forecasted that epigenetic (DNA sequence independent genetic) study will excite all of us in this era, the beginning of which was marked by the completion of the human genome blueprint. In the same year, we held the 1st Shanghai International Conference in Development and Diseases, offering 12 oral presentations (half given by scientists from abroad) to promote epigenetic study in China (October 2003, Cell Research, 2003, 13(5)). The US epigenome road map program was launched in 2008, with the aim that global collective efforts will be followed to provide epigenome reference maps of the major types of cells in both human and model organisms. In the same year, we held the 2nd conference[RF1], entertaining over 200 participants with 36 oral presentations by world leading researchers in fields of either epigenetic or genomic sciences

This meeting was also under the name of the 3rd Annual meeting of Asian Epigenome Alliance, which had been formed in Seoul, 2006 to promote regional epigenetic (-omic) researches. Since 2008, we have witnessed rapid maturation of DNA sequencing and mathematical tools, and a number of conceptual breakthroughs in the epigenetic fields. The research efforts from both basic and translational perspective for better understanding/robuster technologies and for better health care are increasingly intensified. We have already entered the most exciting period of epigenetic study in the history.。

To present a snapshot of the key conceptual and technological advances in epigenetic(-omic) field in last few years, we organize The 3rd Shanghai International Conference of Epigenetics and Diseases/The 7th Annual Conference of Asian Epigenome Alliance/Genome Medicine Workshop on Epigenetic(-omic)s in Diseases(from 19th to 22nd April, 2012), in Shanghai.

In this three day conference, 48 leading scientists will speak in 9 sessions to cover most, if not all, recent exceptional advances in the epigenetic field.

To make the latest technologies for epigenetic (-omic) studies known to the meeting participants, three lunch time technological sessions consisting of 6-12 presentations by scientists from selected biotech companies.

This meeting (the third in the series) will keep its tradition as a robust and pleasant forum for knowledge sharing and debate on the hot issues in this field.

We are looking forward to meeting you all in Shanghai, 19-22, April, 2012.

[RF1], http://www.bioon.com/backupfile/shanghaiepigeneticssymposium200807/

The Scientific Program Snapshot

Morning Sessions(Six 30 minute oral presentations):

1, Cancer Epigenetic(-omic)s (20, April), Session 1,

2. Chemistry and biology of the epigenetic signals and key players (21,April). Session 4,

3, Epigenetic(-omic) perspectives of the complex biological systems (2) (22, April), Session 7,

Afternoon parallel session (Five 30 minute oral presentations):

4, Epigenetic(-omic)s in the autoimmune diseases and asthma; (20, April). Session 2

5, Epigenetic(-omic)s in the metabolic or psychological disorders; (20, April). Session 3

6, Epigenetic(-omic) perspectives of the complex biological systems (1) (21, April). Session 5

7, High order chromatin structures in the complex biological system; (21, April), Session 6

8, Towards the epigenome reference maps: New conceptual and technological breakthrough (22. April). Session 8

9, Non-coding RNAs in development and diseases;(22, April). Session 9

LIST OF SPEAKERS

Confirmed:

1, Yi Zhang (USA)
2, Assam El-Osta (Australia)
3, Bin-Tean Teh (Singapore)
4, Erwei Song (China)
5, Toshikazu Ushijima (Japan)
6, Yutaka Kondo (Japan)
7, Young-Joon Kim (Korea)
8, NG Huck Hui (Singapore)
9, Susan J. Clark (Australia)
10,Xuebiao Yao(China)
11,Bin Ren (USA)
12,Guoliang Xu (China)
13.Ruiming Xu (China)
14.Chunming Ding (Singapore)
15.Howard Cedar (Israel)
16,Hiroyuki Sasaki (Japan)
17,Tohru Nakano(Japan)
18,Kin-ichi Nakashima(Japan)
19,Jonathan Loh (Singapore)
20,Yijun Qi (China)
21,Soo Jong Um(Korea)
22,Dae-Youp Lee (Korea)
23,Yoo-Sun Noh(Korea)
24,Jingde Zhu(China)
25, Jonathan Loh (Singapore)
26, Haruhiko Siomi(Japan)
27, Taiping Chen (US)
28, Kazuya Iwamoto (Japan)
29, Yi-Ching Wang (Tainan)
30, Li-Jung Juan (Taibei)
31, Craig L. Peterson(US)
32, Moschel Surf (Canada)
33, Esteban Ballestar(Spain)
34, Shumin Zhao(China)

35. Dirk Schübeler (Switzerland)
36, Hongjun Song (USA)
37, Shuk-Mei Ho(USA)
38, Xuetao Cao (China)
39, Isabelle Mansuy (Germiy)
40, Marcus E Pembrey (UK)
41, Jing-Dong Jackie Han(China)

ORGANIZERS

Jingde Zhu
Shanghai Cancer Institute/Renji Hospital,
Shanghai Jiaotong University
Shanghai, China

Lin He
Shanghai Fudan University
Institutes of Biomedical Sciences
Shanghai, China

ORGANIZERS

Jingde Zhu (Shanghai, China)

Lin He(Shanghai, China)

Rebecca Furlong (Genome Medicine, UK)

Toshikazu Ushijima(Japan)

Youngjoon. Kim (Korea)

Huck-Hui Ng (Singapore)

Yi Zhang (US)

14.30-15.00	Break
15.20-15.50	
15.50- 16.20	
16.20-16.50	Esteban Ballestar
13.30-16.50	Parallel Session 3, Epigenetic(-omic)s in the metabolic or psychological disorders; Chairman: Assam El-Osta and Moshe Syzf
13.30-14.00	Moshe Syzf
14.00- 14.30	Isabelle Mansuy
14.30-15.00	Kazuya Iwamoto
15.20-15.50	Break
15.50- 16.20	Shumin Zhao
16.20-16.50	Assam El-Osta
	April 21,
Session 4	Chemistry and biology of the epigenetic signals and key players Chairmen: Yi Zhang and Ruiming Xu
08.20-08.50	Yi Zhang
08.50-09.20	Kinichi Nakashima
09.20-09.50	Xuebiao Yao
09.50-10.10	Break
10.10-10.40	Yi-Ching Wang
10.40-11.10	Ruiming Xu
11.10-11.40	Yoo-Sun Noh
11.50-13.20	Lunch time company talks(2)
13.30-16.50	Parallel Sessions 5, Epigenetic(-omic) perspectives of the complex biological systems (1) Chairmen: Hiroyuki Sasaki and Hongjun Songi
13.30-14.00	Hiroyuki Sasaki
14.00- 14.30	Hongjun Song
14.30-15.00	
15.20-15.50	Break
15.50- 16.20	Tohru Nakano
16.20-16.50	Kin-ichi Nakashima
13.30-16.50	Parallel Sessions 6, Higher order chromatin structure of the complex biological system; Chairman: Craig L. Peterson(USA)) and Soo Jong Um(Korea)
13.30-14.00	Craig L. Peterson
14.00- 14.30	
14.30-15.00	Break

Jingde Zhu(China)

Guoliang Xu (China)

Erwei Song (China)

Xuebiao Yao (China)

Yijun. Qi(China)

Ruiming Xu(China)

Xuetao Cao(China)

Shimin Zhao(China)

AGENDA

April, 19	
09.00-23.00	Registration, Pine City Hotel（青松城大酒店）
April, 20	
08.10-8.20	Opening of conference
08:41-12:00	Epigenetics (-omics) in Development
	Genome Medicine Workshop on Epigenetics in Diseases
08.20	Session 1, Epigenetics(-omics) in Cancer Chairmen Dr. Jingde Zhu and Dr. Toshikazu Ushijima
08.20-08.50	
08.50-09.20	T. Ushijima
09.20-09.50	Bin-Tean Teh
09.50-10.10	Break
10.10-10.40	Y. Kondo
10.40-11.10	Li-Jung Juan
11.10-11. 40	Jingde Zhu
11.40-13.20	The lunch time Company presentation 1;
13.30-16.50	Parallel Session 2, Epigenetic(-omic)s in the autoimmune diseases and asthma; Chairman :Esteban Ballestar(Spain) and Shuk-Mei Ho (USA)
13.30-14.00	Shuk-Mei Ho
14.00- 14.30	

15.20-15.50	Taiping Chen
15.50- 16.20	Soo Jong Um
16.20-16.50	
	April 22,
08.20- 11.40	Session 7: Epigenetic(-omic) perspectives of the complex biological systems (2) Chairman: Guoliang Xu and Dr. Howard Cedar
08.20-08.50	Dirk Schübeler
08.50-09.20	Yasuhiro Yamada
09.20-0 9.50	Guoliang, Xu
09.50-10.10	Break
10.10-10.40	Howard Cedar
10.40-11.10	Chunming Ding
11.10-11.40	Jonathan Loh
11.40 -13.20	The lunch time Company presentation 3;
13.30-16.50	Parallel Sessions 8, Non-coding RNA in development and diseases; Chairman: Yijun Qi and Haruhiko Siomi
13.30-14.00	Yijun Qi
14.00- 14.30	Erwei Song
14.30-15.00	
15.20-15.50	Break
15.50- 16.20	Haruhiko Siomi
16.20-16.50	
13.30-16.50	Parallel Sessions 9 Towards the epigenome reference maps: New conceptual and technological breakthrough Chairman: Youngjoon Kim and Huck-Hui Ng
13.30-14.00	Bin Ren
14.00- 14.30	Youngjoon Kim
14.30-15.00	Susan Clark
15.20-15.50	Break
15.50- 16.20	
16.20-16.50	Huck-Hui Ng
16.50- 18.00	Closing of conference