行政院國家科學委員會專題研究計畫　成果報告

核心設施-微陣列基因體醫學核心實驗室 III

計畫類別：個別型計畫
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執行期間：93 年 01 月 01 日至 94 年 04 月 30 日
執行單位：國立臺灣大學醫學院內科

計畫主持人：楊泮池
共同主持人：陳健尉

報告類型：完整報告
報告附件：出席國際會議研究心得報告及發表論文
處理方式：本計畫可公開查詢

中　華　民　國 94 年 8 月 8 日

一. ABSTRACT:

Microarray technology is the central platform for functional genomics and translational research in the post-genomic era. Our main goal is to establish an up-to-date microarray core facility, dedicated to provide high quality microarrays, technical supports and services to researchers in genomic medicine nationwide. Access to this high quality microarray will allow our researchers to be on the cutting edge of genetic research, focus on microarray-based gene expression profiling to explore the pathogenic mechanism of human diseases. The microarray technology is particularly important to clinical medicine in post-genomic era. It will provide high throughput and valuable insights into differences in an individual's disease as compared with constitutional mRNA expression. The microarray information can provide tissue-specific disease signatures and therefore, can improve disease diagnosis, disease classification, prognosis evaluation, identify biomarkers, individualized patient treatment and improve treatment outcome. Although the cDNA microarray is extremely powerful, the current application is still limited. The major obstacles are its high cost and difficulty in maintaining good quality microarray and experiment. The purpose of this project presented here is to establish the Core Lab and libraries for high quality service of microarray under the reasonable price. The core facility will provide services including target labeling, microarray hybridization, colorimetric and fluorescence detections, image digitization, and cluster analysis. In addition, the services of custom-made chips including membrane- and glass-format microarray are also provided. According to the work capacity, microarray core facility will open for the investigators of academic and research institution participated in National Research Program of Genomic Medicine to apply. The core facility has been established in National Taiwan University College of Medicine for more than four years. Also, the Core Lab offered related research consultation and education training to medical campus. National Science Council supports our core facility from 2002 to set up the "Microarray Core Facility for Genomic Medicine", which offers nation-wide microarray services right away. The microarray core facility has provided complete microarray services for dozens of institutions, including the researchers of Taiwan University, Chung-Shan, Yang-Ming University, Chang-Geng University, Chung-Shan Medical University, and so on, for 2,853 pieces of microarray membranes including human, mouse, and custom-made chips. There are still hundreds of chips waiting for preparation. We had published 7 papers on SCI journals and submitted 3 papers. The users of this core facility also had published 5 papers on SCI journals and submitted 2 papers (*see publication*). We will provide services by the enrolled order and work capacity. To provide a large number and swift microarray services and develop new microarray format such as cell-based siRNA and promoter screening microarrays, the additional equipment and personnel are essential. The Web address of Microarray Core Facility is http://microarray.mc.ntu.edu.tw in which containing application procedure and working flow path, applicants can apply for services on-line and download the application form.

微陣列是發展及應用較為成熟的生物晶片技術之一; 是後基因時代基因體醫學研究之重要平台, 此晶片技術已廣泛的應用於各領域的基礎研究, 亦將直接或間接的應用於疾病之診斷、

分類、疾病之預後評估，並改善疾病之治療。由於基因晶片的設備及成本高昂，導致此技術無法廣為應用於各領域之研究。本計劃之目的為設立微陣列核心實驗室及基因庫，將以合理價格提供高品質之人類及老鼠基因微陣列晶片全套性且完整性實驗服務，包括核酸標記、雜交反應、呈色偵測、影像分析、數值擷取及叢集分析，另外並代為製作各式晶片。核心實驗室將依最大工作能量，提供參與基因體醫學國家型科技計畫之各學術及研究機構研究人員申請使用。

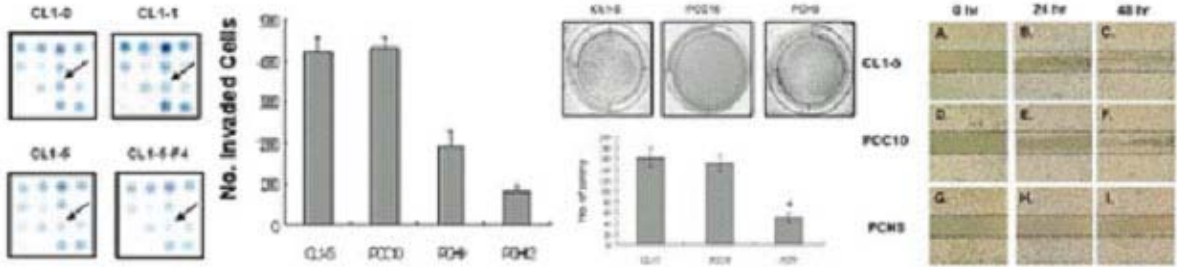
本核心實驗室已於台大醫學院設置四年有餘，並提供醫學校區相關的研究諮詢與教育訓練。九十一年度受國科會補助成立「微陣列基因體醫學核心實驗室」，並立即提供全國性的微陣列服務，為國內能完整提供基因微陣列服務的核心實驗室之一。自從九十一年八月受國科會補助開始對外服務後，目前已提供台大、陽明、中山、長庚、中山醫學等大學超過 2,853 片人類、老鼠及代製晶片，後續登記要求服務的更高達數百片，將依登記先後及實驗室製作容量提供服務。我們已在國際期刊發表七篇 SCI 文章，另有三篇正在審查中；核心設施使用者也發表了五篇 SCI 文章並有兩篇審查中(如 Publication 段落)。為能提供高品質、大量且快速的微陣列服務並發展新的微陣列格式，如細胞 siRNA 及啟動子微陣列等，增購相關設備及增聘研究人員則是必要的。為提昇基因微陣列之教學及人員操作訓練，我們編撰基因微陣列操作儀使用手冊及基因微陣列資料分析實務手冊〈請見附件〉。提供使用者深入瞭解基因微陣列儀器之操作及資料分析。我們並建立基因體醫學核心實驗室網站〈http://microarray.mc.ntu.edu.tw〉，內含申請程序及作業流程，可供使用者上網申請並下載表格。研究同仁可直接上網申請服務，找尋資訊或查詢資料

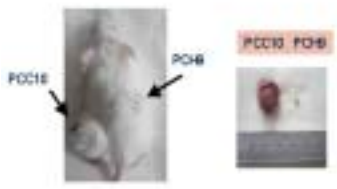
二. Preliminary Studies and Progress Report

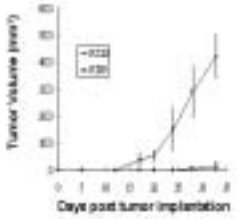
Preliminary Studies

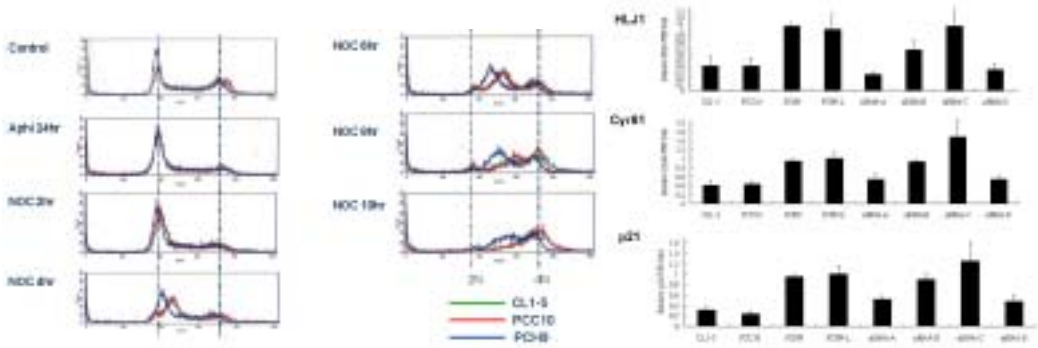
1. Discovery of tumorigenesis-related genes

a. HLJ-1



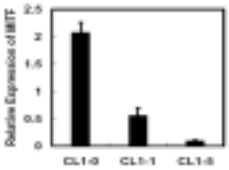


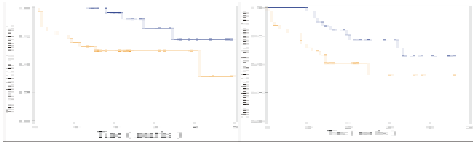




We have identified a novel candidate gene HLJ-1 involving tumor metastasis using microarray technology. Immuno-fluorescent staining indicated that HLJ-1 protein was located in nucleolus and focused on chromosomes at anaphase. The transfectants with HLJ-1 possessed the less ability of *in vitro* invasion, migration, and colony formation. Tumorigenic analyses in SCID mice showed that the expression of HLJ-1 could suppress the tumor growth and reduce the tumor mass volume. The results of real-time quantitative reverse-transcription polymerase chain reaction (RTQ-RT-PCR) also revealed that HLJ-1 was expressed more in normal tissues (80 %) than in tumor ones (20 %), furthermore, significantly correlated with survival and relapse in lung adenocarcinoma patients. All the results suggested that HLJ-1 is a potential invasion/tumor-suppressor gene. HLJ1 inhibits cell proliferation by blocking G1/S transition. To synchronize, the cells were serum-starved and 0.5ug/ml of aphidicolin was added to block the cells at G0/G1for 24hr. Next, cells were stimulated with 10% FBS and the same times, 40ng/ml Nocodazole was added to block the cells at G2/M. The cells were harvested at various time points, fixed with 70% cold ethanol and stained with propidium iodide (PI) for DNA content analysis by flow cytometry. Results showed that the CL1-5 and PCC10 control cells entered S phase 2 hr after being released from the G1/S block, while HLJ1 tranfected cells had just started DNA synthesis at 4 hr after the removal of aphidicolin. These data suggest that HLJ1 may block or retard initiation of DNA synthesis. In further studies, we investigated in more responsible for this growth suppression. We found that HLJ1 suppresses the growth of non- small lung cancer cells prominently up-requlated expression of cyr61 and p21.

b. MITF





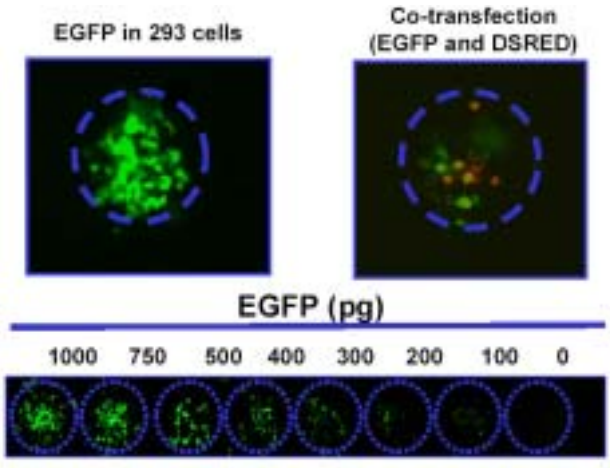
The clinicopathological characteristics of tumors with high and low gene expression of MITF

Clinicopathological characteristic	MITF expression HIGH	LOW	p-value
Gender			
Male	27	25	0.2155
Female	4	6	
Stage			
stage1 and 2	22	15	0.0411
stage3 and 4	9	16	
Survival (>2 years)			
Yes	27	19	0.0162
No	4	12	
Metastasis (>2 years)			
No	24	15	0.063
Yes	10	16	

We identify tumorgenesis-associated genes using cDNA microarrays containing 31104 nonredundant expressed sequence tag clones. Among identified targets, microphthalamia-associated transcription factor (MITF) was noticed, whose expression was negatively correlated with cell line invasiveness and tumorgenesis. MITF encodes a transcription factor that is essential for normal melanocyte development and appears to regulate expression of several pigmentation genes. The transcriptional expression analysis of MITF using quantitative RT-PCR demonstrated a tight correlation between its expression level and clinical characteristics in lung cancer specimen. MITF was lower expressed in cancer tissues compared to the counterparts of normal tissues and its expression level also significantly corrected to survival and disease free of cancer patients.

2. Development of cell-based microarray and viral chip

a. Cell-based microarray

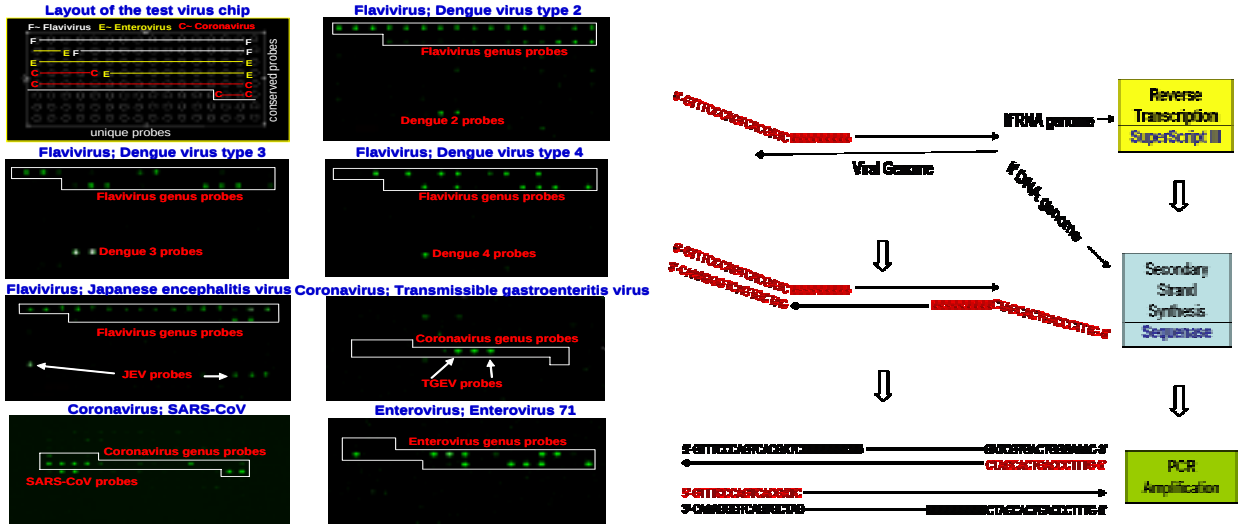


Cell-based microarray performed by reverse transfection of plasmid DNAs in glass slides layered with HEK293 cells.

First, we used a recently developed new technique so-called reverse-transfection to develop cell-based microarray. The EGFP-expressed vector in 0.2%gelatin solution printed onto a glass slide with varied

concentration (100pg to 1000pg) by a solid pin arrayer about 500 um apart. The fluorescence expression levels of cell clusters in a microarray were proportional to the amount of vector DNA printed onto the slide. When the cells were reverse transfected with pEGFP-expressed plasmid and pDSRED-expressed plasmid at the same spot printed with both plasmids, the fluorescence microscopy image showing green and red signals indicated that the co-transfection is possible in cell-based microarray.

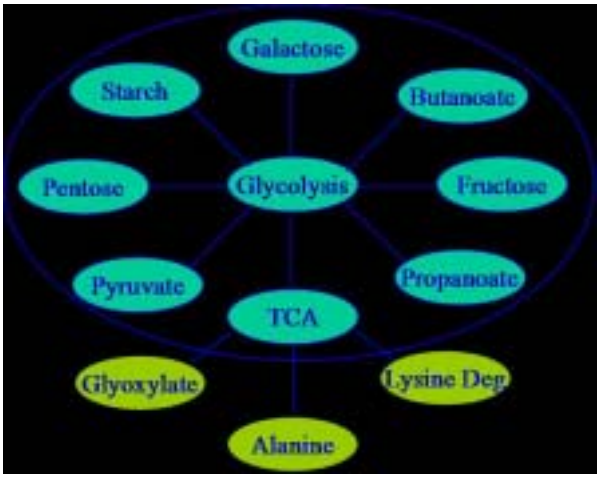
b. Viral chip



Experimental results for the virus chip of seven viral samples (left panel) and illustration of viral genome amplification protocol (right panel).

To verify the approach of probe design, 128 70-mer oligonucleotides covering three viral genera (Coronavirus, Flavivirus, and Enterovirus) were synthesized and spotted on glass slides. Seven viral genomes (SARS-CoV, transmissible gastroenteritis virus, Japanese encephalitis virus, Dengue virus II/III/IV, and Enterovirus 71) extracted from infected cell cultures were individually labeled with fluorescent dye and hybridized to the oligonucleotide microarray. The experimental results indicate that only the correct spot/target pairs yield detectable signals (left panel). We have also established a standard operating procedure (SOP) to amplify and detect unknown viruses in clinical specimens. The SOP applies to detection of viruses of either DNA or RNA genomes (right panel). The current detection limit of the virus chip is less than 100 virus particles for SARS-CoV.

3. Development of pathway analysis tool



Simulation result of PathBLAST using the published diauxic shift experiments.

We tested the utility of **PathBLAST** initially with the data from the diauxic shift experiments (38), which have become the "gold standard" for the application of expression arrays to the study of metabolism. The experiment investigates the temporal program of gene expression accompanying the metabolic shift from fermentation to respiration that occurs when fermenting yeast cells, inoculated into a rich medium containing glucose (20 g/L), turn to aerobic utilization of the ethanol produced during the fermentation after the fermentable sugar is exhausted. The authors made whole-genome hybridization experiments comparing gene expression at seven timepoints (T_1-T_7) to characterize the changes in gene expression that take place during the diauxic shift.

We used **PathBLAST** to rank the statistical significance of the changes observed in the genes organized according to the logic of the 92 KEGG metabolic pathways during the diauxic shift. **PathBLAST** employs the fold-change weighted scoring test to measure the probability that a pathway is significantly altered, for any specified threshold (usually the cutoff is <= 0.05). The results from **PathBLAST** indicate that the main positively affected pathways during the diauxic shift are oxidative phosphorylation, the citrate cycle, the electron transport system complexes II and IV, and pyruvate metabolism. The negative values of the genes for ribosomal proteins and RNA polymerase are also in agreement with the progressive reduction in cellular metabolism, DNA and RNA synthesis, and entry into stationary phase, which are expected with the exhaustion of the sugars and alternative carbon sources (see above Figure). The above *in-silicon* simulation has fully demonstrates the validation of this approach on the diauxic shift experiments and its potential to help interpret the results from one or more experiments, by examining differential expression.

4. Development of home-made oligonucleotide microarray

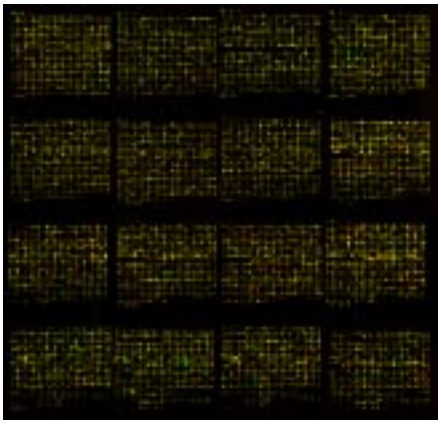
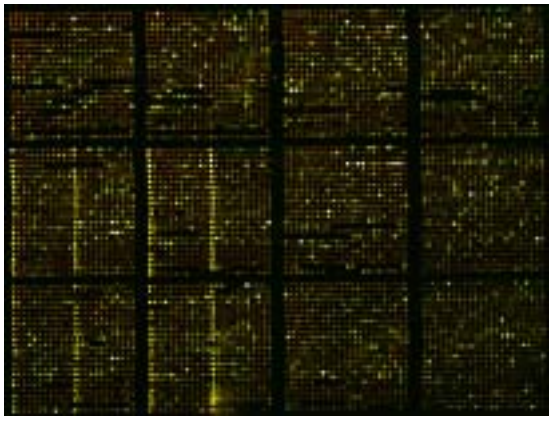

(A)

(B)

Figure 1. (A) A hybridization image of 150mer gene-specific oligonucleotide microarray. (B) A part of hybridization image of new 20k oligo microarray.

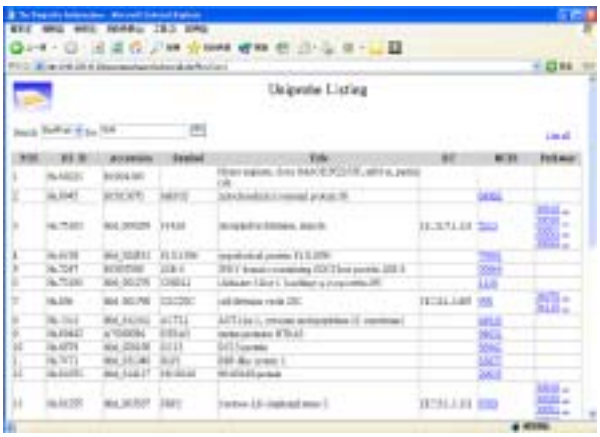


Figure 2. The homepage of UniProbe database.

Home-made types of oligonucleotide microarrays

With the aid of liquid handing robotics and integrated data management system established in our laboratory, we successfully developed a high throughput platform for PCR mass-production. About ~14,000 human gene-specific 150-mer probes have been generated by PCR with genomic DNA and spotted on surface-activated glass slides. An image of the oligonucleotide microarray hybridized with Cy3- and Cy5-labeled samples is shown in Figure1. At the same time a web-based database called UniProbe (http://140.109.43.20/genestamp/uniprobe.htm) is constructed for large scale gene expression analysis. UniProbe is implemented on a MySQL relational database management system. The Web application to query and manage the database is based on PHP. The complete application runs on an Apache web server in a Linux 9 environment. Currently the database contains about 14,000 human named genes, and each gene includes information on empirically validated gene-specific DNA probe and PCR primer sequences for microarray fabrication and for real-time qPCR assays. In addition to the internally generated data, UniProbe provides external links to the National Center for Biotechnology Information (NCBI) LocusLink for more detailed

gene function description, Kyoto Encyclopedia of Genes and Genomes (KEGG) and BioCarta databases for pathway information via UniGene Cluster ID, GenBank accession number, or gene symbol hyperlinks. Figure 2 displays the homepage of UniProbe database. All the gene-specific PCR primer pairs in the database have been empirically verified and can be readily employed in quantitative real-time QPCR assays.

Progress Report

Microarray service

The core facility has been established in National Taiwan University Hospital, National Taiwan University College of Medicine for more than four years and manufactured more than 1,800 pieces of microarray membranes including human, mouse, and custom-made chips. Also, the core Lab offered related research consultation and education training to medical campus. National Science Council supports our core facility two years ago to set up the “Microarray Core Facility for Genomic Medicine”, which offers countrywide microarray services right away.

Our microarray core facility has provided complete microarray services for dozens of institutions, including the researchers of Taiwan University, Yang-Ming University, Chang-Geng University, Chung-Shan Medical University, and so on, for more than 1,000 pieces of microarray membranes including human, mouse, and custom-made chips. There are still hundreds of chips waiting for preparation. We will provide services by the enrolled order and work capacity. To provide a large number and swift microarray services and develop new microarray format such as home-made oligonucleotide chips, viral chips, cell-based, promoter screening microarrays and SiRNA microarrays, and SNP analysis system, the additional equipment and personnel are essential.

The statistical analysis for service is provided as follows to show the working status of core facility, including user list, institution, chip type, number, service items, and so on, in the past three years. Briefly, we have provided 842, 145, and 48 chips of complete microarray services at 2002, 2003 and half a year of 2004, respectively. And we have also provided 1422, 299 and 175 chips at 2002, 2003 and half a year of 2004, respectively. The semi-annual income of 2004 is NT 832,702.

Total chips provided

91年微陣列核心實驗室服務概況

基因體計畫申請者	PI	Membrane
人類基因微陣列薄膜及實驗代工	5	60
代製微陣列薄膜	3	300
核醣核酸放大反應 (RNA amplification)	7	37

非基因體計畫所有申請者	PI	Membrane
人類基因微陣列薄膜及實驗代工	45	563
老鼠基因微陣列薄膜及實驗代工	12	221
血管新生基因微陣列薄膜	8	170
癌轉移基因微陣列薄膜	2	40
代製微陣列薄膜	14	912

92年微陣列核心實驗室服務概況

基因體計畫申請者	PI	Membrane
人類基因微陣列薄膜及實驗代工	1	13
血管新生基因微陣列薄膜	1	60
核醣核酸放大反應	1	12

非基因體計畫所有申請者	PI	Membrane
人類基因微陣列薄膜	6	97
人類基因微陣列薄膜及實驗代工	8	118
老鼠基因微陣列薄膜及實驗代工	2	14
血管新生基因微陣列薄膜	2	142

微陣列核心實驗室服務現況（93年）

基因體計畫申請者	PI	Membrane
人類基因微陣列薄膜 (C5-1)	2	11
人類基因微陣列薄膜及實驗代工 (C5-2)	8	41

非基因體計畫所有申請者	PI	Membrane
人類基因微陣列薄膜 (C5-1)	7	72
人類基因微陣列薄膜及實驗代工 (C5-2)	6	32
老鼠基因微陣列薄膜 (C5-3)	1	4
老鼠基因微陣列薄膜及實驗代工 (C5-4)	4	8
代製微陣列薄膜 (C5-5)	3	42
Affymetrix 1 lum chip (C5-9)	4	14
Human Oligochip (C5-10)	1	1

Training and Education

1. Our core facility has given a 50-hour microarray training course including lectures and experimental practices every year in the past three years. The total number of trainees is more than fifty. The schedule of course is provided as followed.
2. We also offer related research consultation and education training anytime if applicants request. We have trained more than 100 persons for microarray experiments and they can successfully carry out microarrays themselves in the past three years.

教育部顧問室九十四年度「生物技術科技教育改進計畫」開課詳細資料

課程名稱：基因體學實驗

課程種類：☑講授課程　☑ 實驗課　　學分數：2

負責老師：楊泮池、陳健尉、俞松良　　人數限制：20

上課地點：基因體醫學中心七樓

課程大綱：

使學員明瞭以往在基因篩選或分析上的方法，並比較近年來新發展的基因篩選或分析技術。基因微陣列的介紹及相關技術的配合與應用是課程的重點，學員於此課程亦可知悉未來此領域的發展趨勢為何，同時，也會介紹及示範商品化的基因晶片的操作與分析流程，預期此技術未來將廣泛應用於臨床樣本篩檢，為能應用於微量之檢體，課程中將討論試管增值及核酸增值等實驗技術，為使學員能更加了解及認識基因晶片，課程提供實作名額供學員修習，除增加學員在此領域的專業知識外亦可使學員具實際的實驗操作能力，期能增進基礎研究與臨床應用，並符合當前時代之脈動與推展本中心於生物醫學界之特色。

課程表

日期	時間	主　　題	授課老師
7/4	13:00-14:30	基因微陣列之製備及晶片檢測	陳健尉
	14:30-18:00	塞核酸晶片製作(示範教學)	陳健尉
7/5	13:00-14:30	微陣列技術之發展與現況	楊泮池
	14:30-18:00	RNA 萃取(實際操作)	陳健尉
7/6	13:00-14:30	玻片式晶片的製作及訊號偵測	晏孟勳
	14:30-18:00	RNA 定量(毛細管電泳生物分析儀、示範教學)與塞核酸晶片(實際操作)	陳健尉
7/7	13:00-14:30	微陣列在臨床疾病分類與診斷應用	陳惠文
	14:30-18:00	塞核酸晶片(實際操作)與 Affymetrix 基因晶片(示範教學)	陳健尉
7/8	13:00-14:30	微陣列資料分析	沈林琥
	14:30-18:00	塞核酸晶片(實際操作)與 Affymetrix 基因晶片(示範教學)	陳健尉
7/11	13:00-14:30	生物資訊之介紹:Pathway analysis	周正中
	14:30-18:00	塞核酸晶片與 Realtime PCR(實際操作)	陳健尉
7/12	13:00-14:30	細胞晶片與 RNAi 晶片之原理與應用	俞松良
	14:30-18:00	訊號擷取	陳健尉
7/13	13:00-14:30	國外微陣列技術之發展	莊耀宇
	14:30-18:00	微陣列資料分析	陳健尉
7/14	13:00-14:30	基因微陣列的後續實驗	陳健尉
	14:30-18:00	微陣列資料分析	陳健尉
7/15	13:00-14:30	綜合討論	陳健尉
	14:30-18:00	微陣列資料分析	陳健尉

(註：1. 因配合上課教師的時間，某些課程可能有異動。2. 因塞核酸晶片實驗必須要較長的時間，所以會有1或2天必須由 13:00-18:00 全天改為實驗課或上課課程)

三. Related publications by using this core facilities:

1. Hong TM, Yang PC, Peck K, Chen JJW, Yang SC, Chen YC, and Wu CW. (2000). Profiling the Down Stream Genes of Tumor Suppressor PTEN in Lung Cancer Cells by cDNA Microarray. *Am. J. Respir. Cell Mol. Biol.* 23:355-363.
2. Hong TM, Chen JJW, Peck K, Yang PC, and Wu CW (2001). P53 amino acids 339-346 represent the minimal p53 repression domain. *J. Biol. Chem.* 276: 1510-1515.
3. Chen JJW, Peck K, Hong TM, Yang SC, Sher YP, Shih JY, Wu R, Wu CW, and Yang PC. (2001). Global analysis of gene expression in invasion by a lung cancer model. *Cancer Res.* 61:

5223-5230.

4. Shih JY, Yang SC, Hong TM, Yuan A, Chen JJW, Yu CJ, Chang YL, Lee YC, Peck K, Wu CW, and Yang PC. (2001). Collapsin response mediator protein-1 and the invasion and metastasis of cancer cells. *J. Natl. Cancer I.* 93: 1392-1400.
5. Chen HW, Chen JJW, Tzeng CR, Li HN, Chang SJ, Cheng YF, Chang CW, Wang RS, Yang PC, and Lee YT. (2002). Global Analysis of Differentially Expressed Genes in Early Gestational Decidua and Chorionic Villi using a 9,600 Human cDNA Microarray. *Mol. Hum. Reprod.* 8: 475-484. (Cover story)
6. Shih JY, Lee YC, Yang SC, Hong TM, Huang CY, and Yang PC. (2003). Collapsin response mediator protein-1: a novel invasion-suppressor gene. *Clin Exp Metastasis.* 20(1): 69-76.
7. Chen JJW, Yao PL, Yuan A, Hong TM, Shun CT, Kuo ML, Lee YC, and Yang PC. (2003). Up-regulation of Tumoral Interleukin-8 Expression by Infiltrating Macrophages: Its Correlation with Tumor Angiogenesis and Patient Survival in Non-Small Cell Lung Cancer. *Clin. Cancer Res.* 9: 729-737.
8. Chen HW, Yu SL, Chen JJW, Li HN, Lin YC, Yao PL, Chou HY, Chien CT, Chen WJ, Lee YT, and Yang PC. (2004). Anti-Invasive Gene Expression Profile of Curcumin in Lung Adenocarcinoma Based on a High Throughput Microarray Analysis. *Mol. Pharmacol.* 65: 99-110.
9. Yang WC, Chen HW, Au HK, Chang CW, Huang CT, Yen YH, and Tzeng CR. (2004). Serum and endometrial markers. *Best Pract Res Clin Obstet Gynaecol.* 18: 305-318.
10. Yu SL, Chen HW, Yang PC, Peck K, Chen JJW, and Lin FY. (2004). Differential Gene Expression in Gram-Negative and Gram-positive Sepsis. *Am. J. Resp. Crit. Care Med.* 169:(10) 1135-1143.
11. Chen HW, Yu SL, Chen WJ, Yang PC, Chien CT, Chou HY, Li HN, Peck K, Huang CH, Lin FY, Chen JJW and Lee YT. (2004). Dynamic Changes of Gene Expression Profiles during Postnatal Heart Development in Mice. *Heart* 90: 927-934.
12. Kuo Yuan, Tse-Ming Hong, Jeremy Chen, Wan-Hua Tsai, and Ming T Lin (2004). The Impact of Low-dose Busulfan on Clonal Dynamics in Non-Human Primates *Blood* 104: 1025-1033.
13. Yuan A, Chen JJW, Yao PL, and Yang PC. (2005) The role of interleukin- 8 in cancer cells and microenvironment interaction. *Frontier in Bioscience*. 10: 853-865.
14. Chen JJW, Lin YC, Yao PL, Yuan A, Chen HY, Tsai MF, Chen CH, and Yang PC. (2005). Tumor-Associated Macrophages: The Double Edge Sword in Cancer Progression. *J Clin Oncol* 23: 953-964.
15. Yao PL, Yi-Chen Lin YC, Chen JJW, Wang SS, and Yang PC. (2005). Autocrine and Paracrine Regulation of IL-8 Expression in Lung Cancer Cells. *Am J Respir Cell Mol* (in press).
16. Huei-Wen Chen , Jeremy J.W. Chen, Sung-Liang Yu, Han-Ni Li, Pan-Chyr Yang, Ching-Mao Su, Heng-Kien Au, Ching-Wen Chang, Li-Wei Chien, Chieh-Sheng Chen, and Chii-Ruey Tzeng (2005). Transcriptomic analysis during blastocyst hatching by cDNA microarrray. *Human*

Reproduction (in press).
17. Chen WJ, Chen HW, Yu SL, et al. (2005). Gene Expression Profiles in Hypoxic Preconditioning using cDNA Microarray Analysis: Altered Expression of an Angiogenic Factor, CEACAM-1. Shock (in press).
18. Wang CC, Tsai MF, Hong TM, Chang GC, Chen CY, Yang WM, Chen JJW*, and Yang PC. (2005). The transcriptional factor YY1 upregulates the novel invasion suppressor HLJ1 expression andinhibits cancer cell invasion. Oncogene (in press).
19. Wen-Chien Chou, Hsuan-Yu Chen, Sung-Liang Yu , Linzhao Cheng, Pan-Chyr Yang, Chi V. Dang. (2005) Arsenic suppresses gene expression in promyelocytic leukemia cells partly through Sp1 oxidation. *Blood* (in press).