2008 年中央研究院「年輕學者研究著作獎」得獎人簡介

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得獎著作名稱：(請以申請時之格式填入)

1. Yet-Ran Chen, Hsueh-Fen Juan, Hsuan-Cheng Huang, Hsin-Hung Huang, Ya-Jung Lee, Mei-Yueh Liao, Chien-Wei Tseng, Li-Ling Lin, Jeou-Yuan Chen, Mei-Jung Wang, Jenn-Han Chen, Yu-Ju Chen,*, "Quantitative Proteomic and Genomic Profiling Reveals Metastasis-Related Protein Expression Patterns in Gastric Cancer Cells", *Journal of Proteome Research*(2006), volume 5, p. 2727-2742.
2. Jenn-Han Chen*, Yu-Wang Chang, Chen-Wen Yao, Tzong-Shi Chiueh, Su-Chin Huang, Ko-Yi Chien, An Chen, Feng-Yee Chang, Chi-Huey Wong, and Yu-Ju Chen*,, "Plasma Proteome of Severe Acute Respiratory Syndrome (SARS) Analyzed by Two-dimensional Gel Electrophoresis and Mass Spectrometry", *Proceedings of the national academy of sciences of the United States of America*(2004), vol 101, p.17039-17044.
3. Po-Hung Chou, Shu-Hua Chen, Hsin-Kai Liao, Po-Chiao Lin, Gour Rong Her,

Alan Chuan-Ying Lai, Chun-Cheng Lin*, and Yu-Ju Chen*,, "Nanoprobe-Based Affinity Mass Spectrometry for Selected Protein Profiling in Human Plasma", *Analytical Chemistry*(2005), volume 77, p. 5990-5997.

得獎著作簡介: （2000 字左右）

在人類基因體計畫完成後，大量的基因序列訊息提供了疾病研究一個全新的基礎，但相對於基因，蛋白質往往才是參與細胞生長、分化等生物功能的執行者，利用系統化、高通量及全面性的蛋白質體分析技術可增進我們對於疾病的致病機制有更深入的瞭解，除此之外，也有利於找到可用於早期診斷疾病、建立有效的治療策略或追蹤治療結果的生物標籤；然而現今已知的生物標籤往往缺乏高靈敏度及高專一性，尋找及驗證新的生物標籤是刻不容緩的課題。因此，在後基因時代，可加速開發新的疾病生物標籤(biomarker)的蛋白質體學開啟了一項新領域。

身為臺灣在蛋白質體學研究的先鋒實驗室之一，我們致力於發展以質譜技術為主軸之高靈敏、高通量的蛋白質體學方法，能夠廣泛應用於各種不同來源的樣品，包括臨床上的血液或組織及實驗室培養之細胞，能全面性地分析蛋白體中有潛力的生物標籤。目前本實驗室已經成功建立以質譜為基礎之系統化技術平台，可快速研究複雜、數量眾多蛋白質表現量的差異，在過去幾年中，我們完成了兩項重要的工作，其內容簡述如下:

1.以蛋白體學技術研究嚴重急性呼吸道症候群(SARS)之致病機制

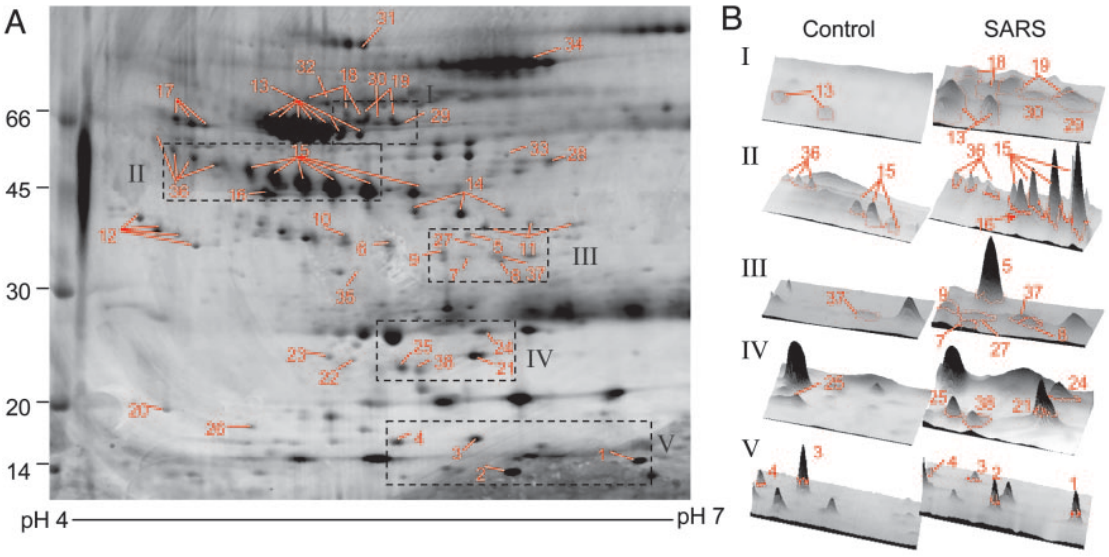
在 SARS 疫情爆發之後，我們與國防醫學院、三軍總醫院及中研院基因體研究中心共同設計了以 SARS 患者血漿為研究材料，利用新興的蛋白質體學技術，分析患者血漿中的蛋白質圖譜，以期找出 SARS 相關之致病機轉。在 SARS 所引發的肺炎中，一些與疾病發展相關的蛋白質會經由因發炎而通透性增加的血管，滲透到全身循環之中。藉由分析血漿的蛋白質圖譜，可以間接地探索 SARS 疾病的特性。將患者血漿以二維電泳的方式，分離血漿中的蛋白質，隨後利用影像處理軟體比對分析 SARS 患者與正常人的血漿蛋白圖譜差異，以找出在 SARS 患者血漿中表現變異的蛋白質，並利用質譜儀技術鑑定出這些蛋白質的身分。在分析了 22 個血漿樣本之後，我們發現共有 38 個血漿蛋白質在 SARS 患者中有明顯的表現差異（見圖一），其中大部分是表現增加的情形。有 15 個蛋白質是在 22 個樣本中均有增加現象，而這 15 個之中又有 7 個不會出現在正常人血漿的蛋白質圖譜中。在經過查証這些蛋白質的功能之後，發現大部分是屬於「急性期蛋白」的血漿蛋白，另外一些則為具有抗氧化作用蛋白、蛋白運送、蛋白酶及其抑制蛋白等。我們並發現了一個曾經被報導在愛滋病患者血液中的蛋白質－ Peroxiredoxin II (Prx II)，又稱為 Natural Killer Enhancing Factor B (NKEF-B)，經過進一步的驗証之後，發現其與溶血現象有密切的關聯性，且可透過Ｔ淋巴細胞分泌。由於在 SARS 患者增加的血漿蛋白質之中，許多都與急性發炎反應有關，而其他包括 Prx II 在內的抗氧化蛋白的濃度也發現比正常人多出許多，這表示

SARS 的致病機轉，可能是透過引發產生嚴重的急性發炎反應以及在肺部所產生的氧傷害，造成 SARS 患者之急性嚴重病情，而這個發現，對未來在 SARS 的治療計劃的擬定上，提供了一個重要參考方向。

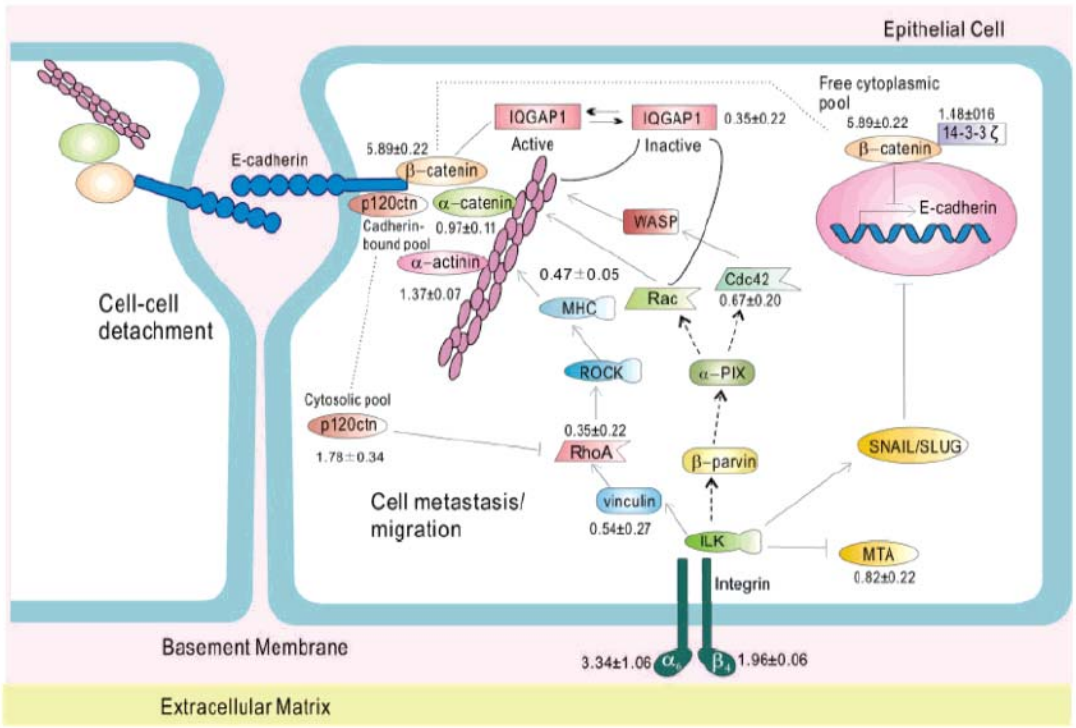
2. 結合同位素標定定量及蛋白體學技術尋找胃癌轉移之標記蛋白質

根據衛生署近 20 年來的統計，胃癌為東亞國家包括我國與日本最常見的癌症，每年都造成數以千計的國人失去寶貴的性命。胃癌的五年存活率低於 20%，若能早期診斷其治癒率及存活率則可大大提高，因此本實驗室結合蛋白質體技術平台、同位素親和性標定試劑 (Isotope-coded affinity tag)以及二維液相層析質譜方法，針對轉移及非轉移胃癌細胞株(TMC-1 和 SCM-1)進行高感度以及高通量的比較性分析，建立了現今最完整的胃癌細胞資料庫，鑑定到本土胃癌細胞 SC-M1 中 926 個和轉移性胃癌細胞 TMC-1 中 909 個蛋白質，在兩者的比較中，並找尋到在兩個細胞中有差異表現之可能胃癌轉移標記之蛋白質，這些不正常大量表達的蛋白質影響包括參與細胞附著(cell-cell adhesion)以及細胞與細胞外基質作用(cell-extracellular matrix interaction)的細胞機制（見圖二），造成正常細胞癌化及轉移。我們更以基因晶片技術以及酵素聚合鏈鎖反應進行驗證，發現這些蛋白質在基因體的變化與蛋白質體的變化是相同的，其中 vimentin 和 galectin 1 在具轉移性的癌細胞中都有過度表現，具有作為癌症轉移之標誌蛋白質的潛力，這些結果將可提供臨床診斷上新的標記蛋白質。

開發高靈敏的蛋白質體技術是未來研究醫學病理的一項重要趨勢，雖然本實驗室已成功建立鑑定生物標籤的技術平台，但我們將持續努力，透過跨領域的合作，結合開發新的蛋白質體技術、生物資訊的統整分析與生物醫學驗証，進一步針對在不同環境及病理條件下細胞、體液或組織的蛋白質體及其轉譯後修飾進行在時間、空間及結構上的分析。



圖一 以二維電泳及質譜鑑定尋找與 SARS 疾病相關的血液中蛋白質（A）二維電泳分離 SARS 病人的血液蛋白質體(B)比對正常人與 SARS 病人的二維電泳，找出在 SARS 病人血液中異常表現的蛋白質並且以質譜鑑定出蛋白質的身分。



圖二 各異常表達蛋白質於包括細胞附著與細胞與細胞外基質作用等各種細胞機制示意圖。蛋白質旁的數字代表該蛋白質的異常變化倍數，此示意圖由各個資料庫(BioCarta, KEGG, and PANTHER)整理所成。

評審簡評：

陳玉如博士使用化學分析研究探討醫學病理像是嚴重急性呼吸道症候群(SARS)和癌細胞，這將是奠定以後醫學與化學分析的結合。其中一篇 PNAS 運用高解析度的二維電泳(2DE)結合質譜技術，發現從未被發現 SARS 裡的血液蛋白質以及對 SARS 樣品提供可靠的數據分析。另外，陳博士運用定量蛋白質體技術結合微陣列晶片的技術建立出複雜的癌細胞的基因組序列，促進了對胃癌細胞成因的瞭解。陳博士的研究橫跨了化學、物理及生物的領域。她的蛋白質體方面的研究可算是台灣首屈一指，並獲得國際上的高度肯定。

2008 Academia Sinica Research Award for Junior Research Investigators

Name: Yu-Ju Chen 	Education: ◆ B.S., National Taiwan University (1992); ◆ Ph.D., Iowa State University, USA (1997); Employer(s)/Job Title(s): ◆ Associate Research Fellow, Institute of Chemistry, Academia Sinica (2005-) ◆ Assistant Research Fellow, Institute of Chemistry, Academia Sinica (1999-2005) ◆ Adjunct Assistant Research Fellow, Genomic Research Center (2004-present) ◆ Adjunct Associate Professor, Department of Chemistry, National Taiwan University (2007--present), Department of Applied Chemistry, National Chia-Yi University (2007--present) ◆ Affiliate Associate Professor, Institute of Bioscience and Biotechnology, National Taiwan Ocean University (2004-Present), Institute of Molecular Biology, National Chung Hsing University (2005-Present) ◆ Postdoctoral Research Associate, National Tsing Hua University (1998-1999); ◆ Postdoctoral Research Associate, Ames Laboratory, U.S.A. (1997); ◆ Distinguished Young Chemists Award, Federation of Asian Chemical Societies (2007). ◆ Young Chemists Award of the Chemical Society Located in Taipei (2006)

1.

Award publications：

1. Yet-Ran Chen, Hsueh-Fen Juan, Hsuan-Cheng Huang, Hsin-Hung Huang, Ya-Jung Lee, Mei-Yueh Liao, Chien-Wei Tseng, Li-Ling Lin, Jeou-Yuan Chen, Mei-Jung Wang, Jenn-Han Chen, Yu-Ju Chen,*, "Quantitative Proteomic and Genomic Profiling Reveals Metastasis-Related Protein Expression Patterns in Gastric Cancer Cells", *Journal of Proteome Research*(2006), volume 5, p. 2727-2742.

2. Jenn-Han Chen*, Yu-Wang Chang, Chen-Wen Yao, Tzong-Shi Chiueh, Su-Chin

Huang, Ko-Yi Chien, An Chen, Feng-Yee Chang, Chi-Huey Wong, and Yu-Ju Chen*,, "Plasma Proteome of Severe Acute Respiratory Syndrome (SARS) Analyzed by Two-dimensional Gel Electrophoresis and Mass Spectrometry", *Proceedings of the national academy of sciences of the United States of America*(2004), vol 101, p.17039-17044.

3. Po-Hung Chou, Shu-Hua Chen, Hsin-Kai Liao, Po-Chiao Lin, Gour Rong Her, Alan Chuan-Ying Lai, Chun-Cheng Lin*, and Yu-Ju Chen*,, "Nanoprobe-Based Affinity Mass Spectrometry for Selected Protein Profiling in Human Plasma", *Analytical Chemistry*(2005), volume 77, p. 5990-5997.

Summary of the Award publications（around 2000 words）:

In the post-genome era, proteomics opens new horizons because it promises to accelerate the discovery of new protein disease markers. The completion of human genome project has catalyzed advances in proteomics to investigate cellular function at the protein level. Proteins are the ultimate effectors of gene function directly participate in biological processes to govern cellular growth, differentiation and survival. Mapping the cellular networks perturbed during disease progression by systematic, high-throughput, genome-wide expression analysis at the protein levels will facilitate our understanding of these processes In addition, the recognition that every disease induces a specific pattern of change in proteomic microenvironments has important clinical implications on the early detection and progression of disease. More precisely, different types of protein markers can be used for early detection of disease, for monitoring effects of therapy, for detecting disease recurrence, and for prognosis. To date, however, there are only few existing protein markers and new biomarkers with good specificity and sensitivity for accurate diagnosis still remain to be discovered.

The development and implementations of proteomic approaches to decipher the complex disease at the molecular level have been our long-term interests. To analyze the complex proteome, mass spectrometry has become one of the most important approached for protein identification and quantitation. Being one of the pioneering proteomics group in Taiwan, we have devoted our efforts to establish new mass spectrometry-based platforms for protein structure analysis and global quantitative protein profiling. In the past few years, our team successfully applied the proteomic approach to decipher the molecular mechanism of some major disease in Taiwan, including the gastric cancer and the complex and untreatable viral disease –severe acute respiratory syndrome (SARS).

Gastric cancer is a leading cause of death worldwide, having an overall 5-year survival rate of less than 10%. Using quantitative proteomic techniques together with

microarray chips, we have established comprehensive proteome and transcriptome profiles of the metastatic gastric cancer TMC-1 cells and the noninvasive gastric cancer SC-M1 cell. Our qualitative protein profiling strategy offers the first comprehensive analysis of the gastric cancer cell proteome, identifying 926 and 909 proteins from SC-M1 and TMC-1 cells, respectively. Cleavable isotope-coded affinity tagging analysis allows quantitation of a total of 559 proteins (with a protein false positive rate < 0.005), and 240 proteins were differentially expressed between the SC-M1 and TMC-1 cells. We identified numerous proteins not previously associated with gastric cancer. Notably, a large subset of differentially expressed proteins was associated with tumor metastasis, including proteins functioning in cell-cell and cell-extracellular matrix (cell-ECM) adhesion, cell motility, proliferation and tumor immunity. These comparative data enabled us to map the disease-perturbed cell-cell and cell-ECM adhesion and Rho GTPase–mediated cytoskeletal pathways. Further validation of a subset of genes suggests the potential use of vimentin and galectin 1 as markers for metastasis. We demonstrate that combining proteomic and genomic approaches not only provides a rapid, robust and sensitive platform to elucidate the molecular mechanisms underlying gastric cancer metastasis but also may identify candidate diagnostic markers and therapeutic targets.

To explore the possible pathogenetic mechanisms involving the progression of SARS, we have analyzed the plasma proteins of 22 different plasma samples from four SARS patients in different time courses. High resolution two-dimensional electrophoresis was applied to profile the plasma proteome from the patients with SARS in different time courses. Based on the high sensitivity sypro-ruby stainned 2DE map of human plasma, and a total of 38 differential spots were found to have dramatic up- and down-regulation. Most of the proteins identified are acute phase proteins, and their presence represents the consequence of serial cascades initiated by SARS-coronavirus infection. Among them, the protein Prx2 have never been identified in plasma before using 2D gel electrophoresis and was chosen for further study by analyzing additional 20 plasma samples from patients with probable and suspected SARS and patients with fever, respectively. It was found to be present before the anti-viral antibody was detected, implicating its significant role in SARS pathogenesis. Our findings indicate that active innate immune responses, along with the oxidation-associated injuries, may play a major role in the pathogenesis of SARS. This study indicated that our proteomic platform can be a fast screening platform to identify disease protein biomarkers as prognostic indicators for patients and provide a new direction for therapeutic development.

The development of sensitive techniques for proteomic profiling has great potential to study the disease mechanism for the next phase of disease diagnosis and

monitoring. We will continue our interdisciplinary efforts to develop new approach to study the temporally, spatially and structurally dynamic proteome in cells, biofluids, and tissues under different environmental or pathophysiological conditions.