GRC

中央研究院

基因體研究中心

The Genomics Research Center
Academia Sinica

Translating scientific discoveries to disease therapeutics and biomedical devices through interdisciplinary approaches

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THE GENOMICS RESEARCH CENTER, ACADEMIA SINICA

Guided by the profound vision of former President Dr. Yuan-Tseh Lee and the founding Director Dr. Chi-Huey Wong, the Genomics Research Center (GRC) was established in 2003. After Dr. Wong was elected the President of Academia Sinica, Dr. Chung-Hsuan Chen assumed the directorship and continues to build a strong research team since 2007.

Composed of both senior scientists as well as energetic and talented junior researchers, GRC research team has expanded to around 40 full-time faculties. Their specialties cover a broad range of fields from physics, chemistry, engineering, computation, biology, to medicine. Among the faculties, we have also an excellent team of specialists to support technology development and to increase innovation capacity. These two unique features enable GRC to facilitate advanced interdisciplinary research. In addition to regular research staff, two other tremendous talent pools, Science Advisory Board (SAB) and Joint Research Fellows, complement our research projects or the Center as a whole. All members in SAB are renowned scientists in the world who advise GRC on both research and strategic planning on a regular basis. More than 40 joint research fellows from major research institutes in Taiwan are also a very valuable asset for projects involving interdisciplinary effort.

To foster young and promising students to join the field of advanced research, GRC currently has joint PhD programs with two top universities-National Defense Medical Center and National Yang-Ming University. GRC faculties also participate in the Taiwan International Graduate Program (TIGP) and other degree programs collaborated by Academia Sinica and local universities. The broad scope of research interests within GRC gives students, research assistants and postdoctors a great opportunity of training in the most cutting-edge fields. GRC will keep cultivating first-class talents to master in the modern disciplines and take the lead in their profession. Distribution of human resources during the past years is shown in Figure 1.

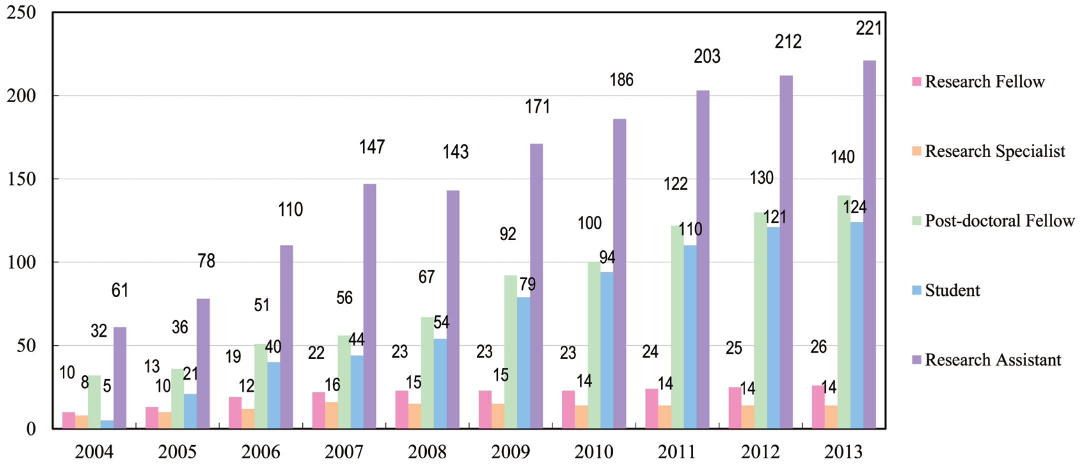
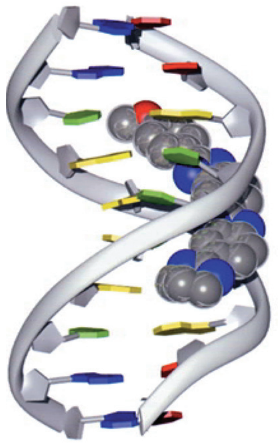


Figure 1. Distribution of human resources of GRC.

In our effort to screen new drug leads for various diseases, GRC has set a chemical library of more than two-million compounds and the most efficient high throughput drug screening facility in Asia. GRC has also established critical facilities for cell biology and biomedical technology development, including mass spectrometer proteomic facility, NMR and X-ray facility for structure determination, microarray, peptide synthesis, high throughput genome sequencer and glycan analysis platforms for genomic research. The animal laboratory and Biosafety Level 3 Laboratory are also among the highlights. These facilities can significantly advance frontier biotechnology development and drug discovery.



The major focus of GRC's research is on the understanding of genes associated with diseases and their functions. Through novel discoveries, powerful diagnosis tools and new therapeutic strategies are expected to be developed. Increased efforts will be placed on the pursuit of fundamental scientific advances through interdisciplinary programs, and the extension of basic discoveries to translational research. Therefore, we organize three research Divisions: Chemical Biology to develop new tools and molecules to target cancer and infectious diseases, Medical Biology to develop translational medicine for cancer biology, stem cell biology, immunobiology and epidemiology, and Physical and Computational Genomics to develop data analysis for drug prediction, and novel biomedical technology development. In addition to these Divisions, GRC has also established the Biotechnology Incubation Center (BIC) for pursuing technology transfer to convert important discoveries into commercial opportunities. To date, BIC has recruited thirteen highly respectable biotechnology companies that licensed technologies from Academia Sinica. Six of these thirteen companies have successfully commercialized proprietary products and hence become independent to build up their own manufacturing facilities. With rapid increase of inventions at Academia Sinica and the more favorable industrial environment for start-up biotech companies in Taiwan, we expect that the number of these successful start-up companies will grow abundantly in the foreseeable future.

Some of the scientific pursuits in GRC with great potential to be among the world leading research include new drug design based on structure study of membrane protein, carbohydrate chemistry and structure biology, the relationship of molecular biology modulation and disease, high throughput technology for drug discovery, infectious disease and vaccine development, immunotherapy, cancer stem cell, epidemiology, evolutionary bioinformatics, biological mass spectrometer development, and fast biomarker search. We continuously strive to make GRC a place that inspires as well as fulfills innovative ideas. Up to 2013, GRC members have published more than 1300 papers and have filed over 250 patent applications. GRC is very competitive compared to all peer institutes in Taiwan and Asia (Figure 2). Its research performance has already matched or been competitive to several international genome related research institutes with high reputation.

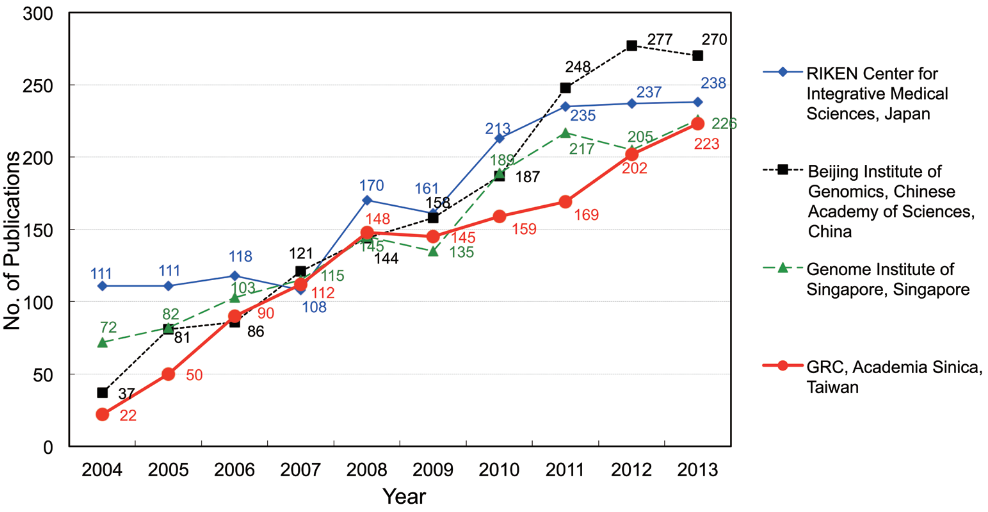


Figure 2. Comparison of publications among relevant institutes (source: *Web of Science, ISI Web of Knowledge,* 2014/6/3).

We will continue to pursue fundamental scientific research and translate the discoveries to disease therapeutics through interdisciplinary approaches. Our future perspective is to play a more crucial role in pharmaceutical and biomedical device industry in Taiwan.

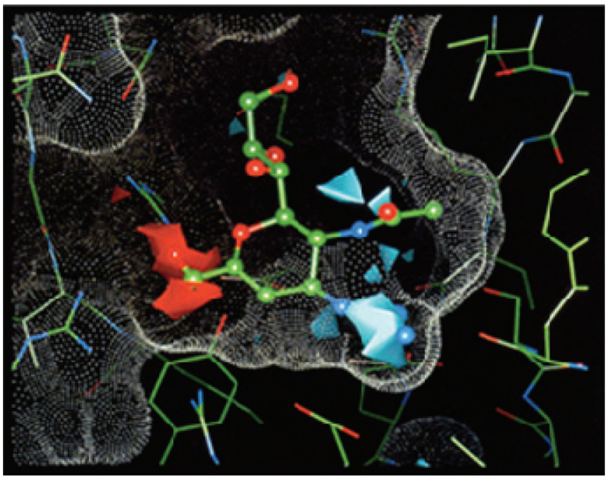
中央研究院基因體研究中心
The Genomics Research Center

中央研究院基因體研究中心於 2003 年元月正式成立，翁啓惠院士應聘回國擔任首屆中心主任，積極規劃研究方向、人才延攬以及進行研究大樓興建。2006 年 10 月翁院士接任院長，主任一職由陳仲瑄博士代理，直至 2007 年 7 月正式任命為中心主任。本中心的任務為「進行基因體與蛋白質體之科學研究，以致力於找尋與確認人類疾病之標的物，發展新穎的治療方式來消弭與克服疾病」，並將所研發的重要成果技術轉移給新創科技公司，予以產業化，帶動台灣生技產業之發展。

基因體研究中心自成立以來，前承本院李遠哲前院長和現任翁院長的大力規劃與推動，成功地延攬多位國內外一流的科學家，以及建立世界級的生技製藥研究設施，有效地整合跨領域的研究平台。人才多元化為中心一大特色，中心專任研究人員有傑出的物理學家、化學家、工程科學家、資訊科學家、生物學家和醫學人才，互相激勵出高創意的研究。本中心諮詢委員會成員都是享譽國際的科學家，其中包括多位美國國家科學院院士和中央研究院院士，他們與中心保持密切連繫，提供具前瞻性的建議，提升中心的研究水準。另中心與國內大學、醫院及研究機構合聘逾 40 位傑出研究人員，加速跨領域研究之進行。此外，中心也以合作學程方式積極從事博士班人才培育工作，目前已有國防醫學院生命科學學程，及陽明大學微生物及免疫學研究所與生化暨分子生物研究所的基因體科學學程。本中心研究人員也參與本院國際研究生學程 (TIGP)，或透過與國內大學合聘、兼任，從事教學，以培育高級研究與技術專才，促進生命科學教育及生技產業的發展。

在 2004 年 11 月中心大樓啓用後，積極建立各項先進的研究設施。目前已建置美國以外全世界最快速的藥物篩選系統，並設立一座龐大的化學藥庫，收集或合成的化合物超過 200 萬種。此外也建置完善的研究設施，包括生物質譜儀、核磁共振結構儀、X 光結晶結構測定儀、微陣列檢測系統、遺傳標記分析儀、醣體分析系統、胜肽合成設施、動物實驗室及三級生物安全實驗室等，使得尖端生技及製藥的研究更具國際競爭力。

本中心針對發展新藥和新興生醫技術設立四個專題中心：(1) 化學生物學，著重於疾病標的物的尋找和新藥合成；(2) 醫學生物學，著重於癌症醫學、幹細胞學、免疫學及流行病學之轉譯研究；(3) 物理與資訊基因體學，著重於生物資訊處理及發展



高創意的生物技術平台；(4) 生技育成中心，負責科技轉移、育成、產業合作與國際交流工作。

本中心近期的研究方向著重於對國人重要疾病的瞭解，進行人類疾病與微生物基因體、蛋白質體、及醣體學結構與功能等研究，以及開發新的技術及藥物。透過前瞻性、創新性、與可行性的跨領域研究，發展高靈敏度的研究平台和儀器，以增進對疾病的瞭解，進而發展新型的藥劑、疫苗、抗生素，因此目前的研究重點為：重大疾病的防治－針對新流感 (H1N1) 及禽流感 (H5N1) 等病毒、泛抗藥性結核菌及金黃色葡萄球菌 (MRSA) 等細菌、乳癌及肺癌等，分析其關鍵生物分子之功能及與疾病的關係；新技術開發－發展超高速新藥篩選系統、醣晶片、全功能生物質譜儀、奈米材料的技術及功能，以及演化基因體研究平台；此外，也進行天然物藥劑及癌症幹細胞的研究，以研發檢測與防治疾病的新策略。

未來的研究課題將以中心具有潛力成為全球領銜之研究領域及相關技術為基礎，繼續更深入及廣泛的探討，包括以膜蛋白研究結構為基礎的新藥開發、醣化學與其生物功能、生物分子修飾與疾病關係的探討、高速檢測與新藥研發技術、傳染病之新藥與疫苗的研發、免疫機能的瞭解、癌症幹細胞研究、流行病學、演化生物資訊、高創意生物質譜的研發，以及找尋生物標的物，期望深耕這些研究，建立國際領先的地位。

本中心研發成果的產業化是由生技育成中心扮演推手角色，透過技術、策略、及管理協助，輔導進駐新創公司共同開發新技術與新產品，使其成為新生物技術、新藥開發或新精密儀器的明日之星，以達到協助產業升級、創造就業機會，促進台灣生技製藥產業的深耕與發展。至今共與 13 家新創公司簽訂合作授權，並進駐生技育成中心，其中 6 家公司已成功研發產品正式離駐。隨著中研院新的研究發明日益增加，及台灣生技新創環境之逐年提昇，在可預見的未來，類似成功案例將會快速成長。

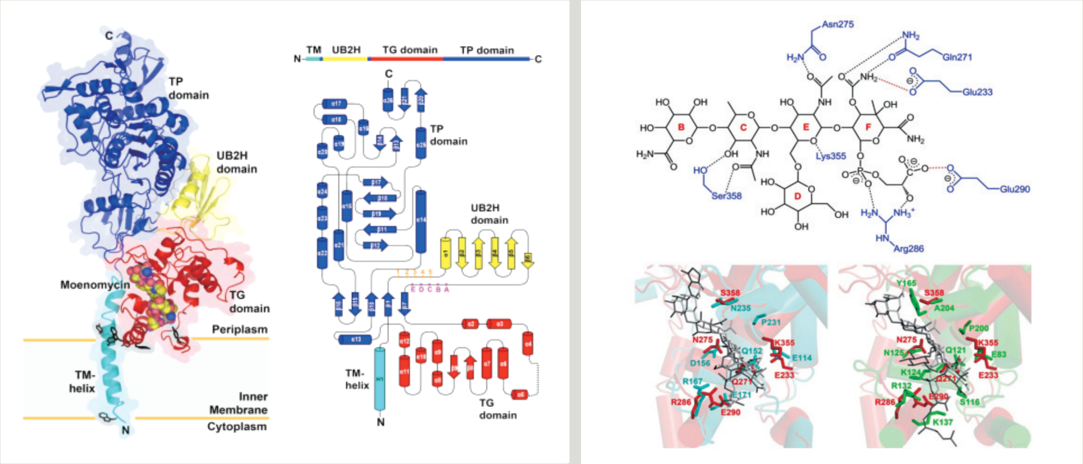
近年來，基因體研究中心已漸趨茁壯成為國內一個跨領域的生技研究重鎮，在前瞻性研究和研發成果的商業化都有長足的發展。自成立以來，本中心建構跨領域的研究平台，在醣體學、疫苗與新藥候選物研發、癌症與幹細胞研究、流行病學、質譜技術開發與演化生物資訊學等各方面，均有突破性的進展，至 2013 年已發表逾 1300 篇國際期刊論文或專著，並提出逾 250 項專利申請。期盼本中心以跨領域的合作平台為基礎，成功整合基礎和應用的研究成果，對台灣的生技製藥研究和產業，都有傑出的貢獻。

MAJOR ACHIEVEMENTS

GRC has devoted itself on the understanding of genes associated with diseases and their functions to develop new diagnosis tools and therapeutic strategies. For the past decade, its researches have made significant breakthroughs on improvement of glycoscience, mass spectrometry, epidemiology, and stem cell biology for biomedical applications, and target identification and therapeutics development for diseases. Key achievements are described as following.

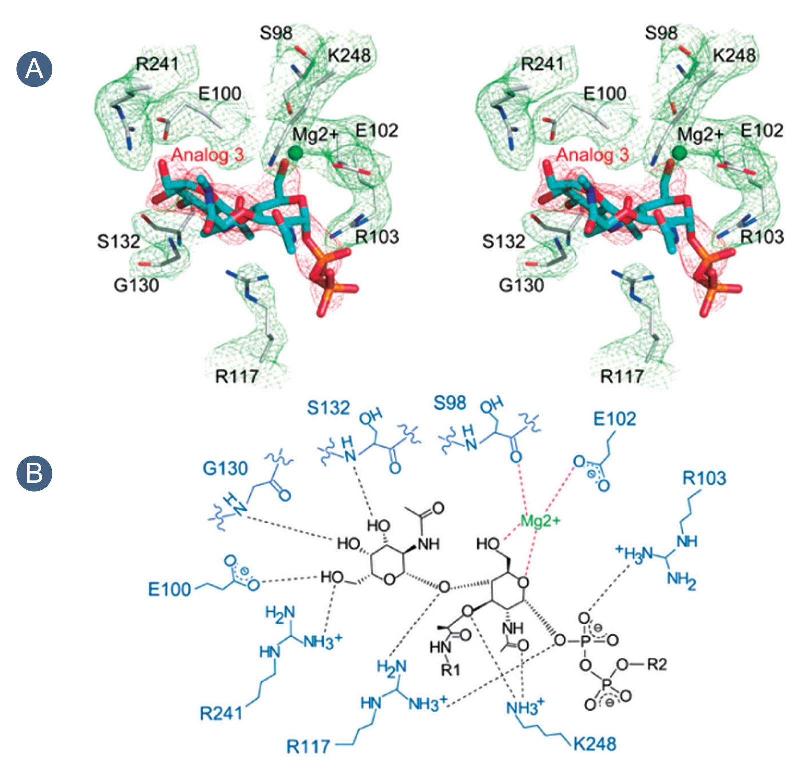
Therapeutics development and target identification for infectious diseases

1. Drug-resistant bacteria have caused serious medical problems in recent years, and the need for new antibacterial agents is undisputed. Transglycosylase, a multidomain membrane protein essential for cell wall synthesis, is an excellent target for the development of new antibiotics. We determined the X-ray crystal structure of the bifunctional transglycosylase penicillin-binding protein 1b (PBP1b) from *Escherichia coli* in complex with its inhibitor moenomycin to 2.2 Å resolution. In addition to the transglycosylase and transpeptidase domains, our structure provides a complete visualization of this important antibacterial target, and reveals a domain for protein-protein interaction and a transmembrane helix domain essential for substrate binding, enzymatic activity, and membrane orientation.



Crystal structure of *E. coli* PBP1b in complex with moenomycin and molecular interaction between moenomycin and transglycosylase provides structural basis for antibiotic discovery

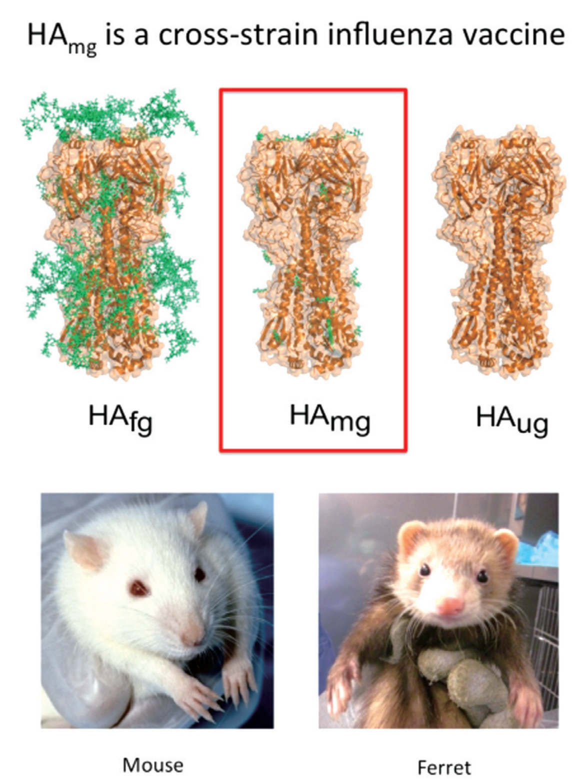
Bacterial transpeptidase and transglycosylase on the surface are essential for cell wall synthesis, and many antibiotics have been developed to target the transpeptidase; however, the problem of antibiotic resistance has arisen and caused a major threat in bacterial infection. The transglycosylase has been considered to be another excellent target, but no antibiotics have been developed to target this enzyme. We also determined the crystal structure of the *Staphylococcus aureus* membrane-bound transglycosylase, monofunctional glycosyltransferase, in complex with a lipid II analog to 2.3 Å resolution. Our results showed that the lipid II-contacting residues are not only conserved in WT and drug-resistant bacteria but also significant in enzymatic activity. Mechanistically, we proposed that K140 and R148 in the donor site, instead of the previously proposed E156, are used to stabilize the pyrophosphate-leaving group of lipid II, and E100 in the acceptor site acts as general base for the 4-OH of GlcNAc to facilitate the transglycosylation reaction. This mechanism, further supported by mutagenesis study and the structure of monofunctional glycosyltransferase in complex with moenomycin in the donor site, provides a direction for antibacterial drugs design.



Stereo and schematic view of interaction between
Staphylococcus aureus transglycosylase and Lipid II analog

- Crystal structure of the membrane-bound bifunctional transglycosylase PBP1b from *Escherichia coli. Proc Natl Acad Sci USA*, 2009, *106*, 8824-9.
- Effect of the peptide moiety of lipid II on bacterial transglycosylase. *Angew Chem Int Ed*, 2012, *51*, 10123-6.
- Crystal structure of *Staphylococcus aureus* transglycosylase in complex with a lipid II analog and elucidation of peptidoglycan synthesis mechanism. *Proc Natl Acad Sci USA*, 2012, *109*, 6496-501.

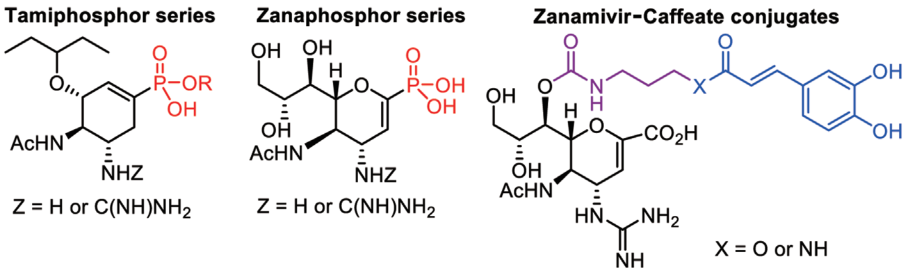
2. The 2009 H1N1 pandemic and recent human cases of H5N1, H7N9 and H6N1 in Asia highlight the need for a universal influenza vaccine that can provide cross-strain or even cross-subtype protection. We showed that recombinant monoglycosylated hemagglutinin (HA_{mg}) with an intact protein structure from either seasonal or pandemic H1N1 can be used as a vaccine for cross-strain protection against various H1N1 viruses in circulation from 1933-2009 in mice and ferrets. In the HA_{mg} vaccine, highly conserved sequences that were originally covered by glycans in the fully glycosylated HA (HA_{fg}) are exposed and were thus better engulfed by dendritic cells (DCs), stimulated better DC maturation, and induced more $CD8^+$ memory T-cells and IgG-secreting plasma cells. Single B-cell RT-PCR followed by sequence analysis revealed that the HA_{mg} vaccine activated more diverse B-cell repertoires than the HA_{fg} vaccine and produced antibodies with cross-strain binding ability. In summary, the HA_{mg} vaccine elicits cross-strain immune responses that may mitigate the current need for yearly reformulation of strain-specific inactivated vaccines. This strategy may also map a new direction for universal vaccine design.



Vaccination of monoglycosylated hemagglutinin induces cross-strain protection against influenza virus infections

- Glycans on influenza hemagglutinin affect receptor binding and immune response. *Proc Natl Acad Sci USA*, 2009, *106*, 18137-42.
- Vaccination of monoglycosylated hemagglutinin induces cross-strain protection against influenza virus infections. *Proc Natl Acad Sci USA*, 2014, *111*, 2476-81.

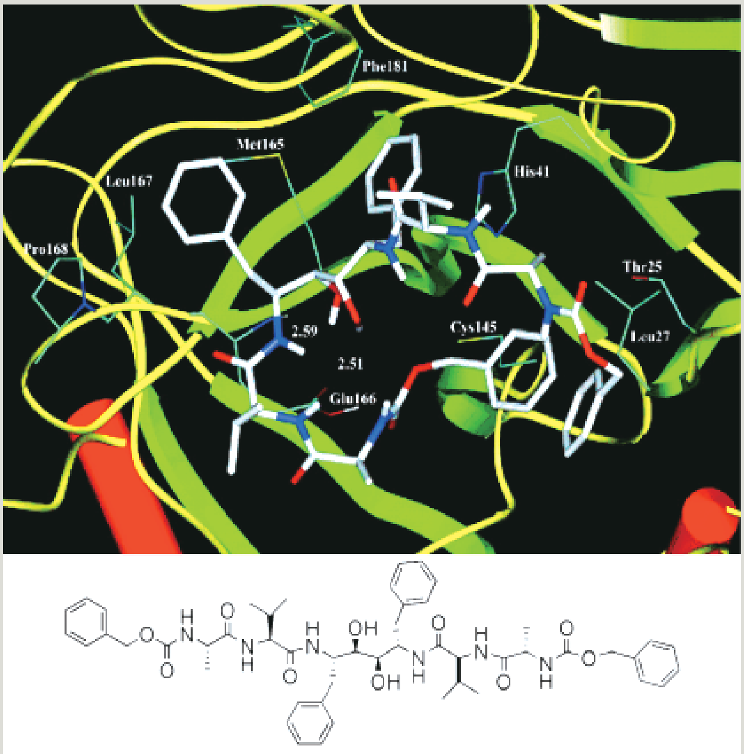
3. Tamiphosphor and zanaphosphor, the phosphonate congeners of oseltamivir (Tamiflu^{TM}) and zanamivir (Relenza^{TM}), are discovered to be effective anti-influenza drugs possessing potent inhibitory activity against the viral neuraminidase. Tamiphosphor, guanidino-tamiphosphor and their monoalkyl esters are orally bioavailable and more effective than oseltamivir in protecting mice against lethal challenge with human and avian influenza viruses, including the tamiflu-resistant H275Y mutant. Novel methods for synthesis of oseltamivir, tamiphosphor, zanaphosphor and their derivatives are also developed. In another aspect, effective bifunctional anti-influenza drugs comprising zanamivir conjugated to anti-inflammatory agents, e.g. caffeic acid, are explored for simultaneous suppression of proinflammatory cytokines. The zanamivir-caffeate conjugates provide remarkable protection of cells and mice against influenza infections.



New anti-influenza drugs targeting the viral neuraminidase

- Synthesis of tamiflu and its phosphonate congeners possessing potent anti-influenza activity. *J Am Chem Soc*, 2007, *129*, 11892-3.
- A concise and flexible synthesis of the potent anti-influenza agents-Tamiflu and tamiphosphor. *Angew Chem Int Ed*, 2008, *47*, 5788-91.
- A practical synthesis of zanamivir phosphonate congeners with potent anti-influenza activity. *J Am Chem Soc* 2011, *133*, 17959-65.
- Enhanced anti-influenza agents conjugated with anti-inflammatory activity. *J Med Chem* 2012, *55*, 8493–501.

4. A cell-based assay with SARS virus and Vero E6 cells were developed to screen more than 10,000 compounds for anti-SARS compounds based on the protection of the SARS-mediated cytopathic effects. About 50 compounds were active with IC50 values ranging at ~1 to 10 μM. Two existing compounds (Reserpine and Aescin) were found active. In addition, some are in clinical development for the treatment for other diseases such as HIV. The HIV protease inhibitor TL-3 was found to be also a potent inhibitor of the SARS viral protease.

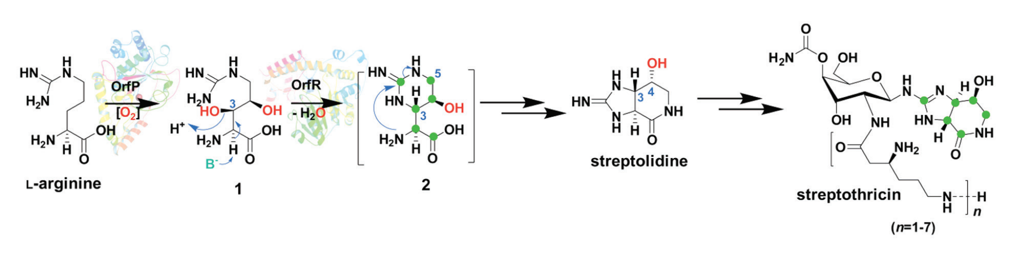


Modeling of TL-3 and SARS-CoV 3CL protease interaction

- Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proc Natl Acad Sci USA*, 2004, *101*, 10012-7.
- Discovery of potent anilide inhibitors against the severe acute respiratory syndrome 3CL protease. *J Med Chem*, 2005, *48*, 4469-73.

5. Streptothricin-F (STT-F), one of the early-discovered antibiotics, consists of three components, a β-lysine homopolymer, an aminosugar D-gulosamine, and an unusual bicyclic streptolidine. The biosynthesis of streptolidine is a long-lasting but unresolved puzzle. A combination of genetic/biochemical/structural approaches was used to unravel this problem. The STT gene cluster was first sequenced from a *Streptomyces* variant BCRC 12163, wherein two gene products OrfP and OrfR were characterized in

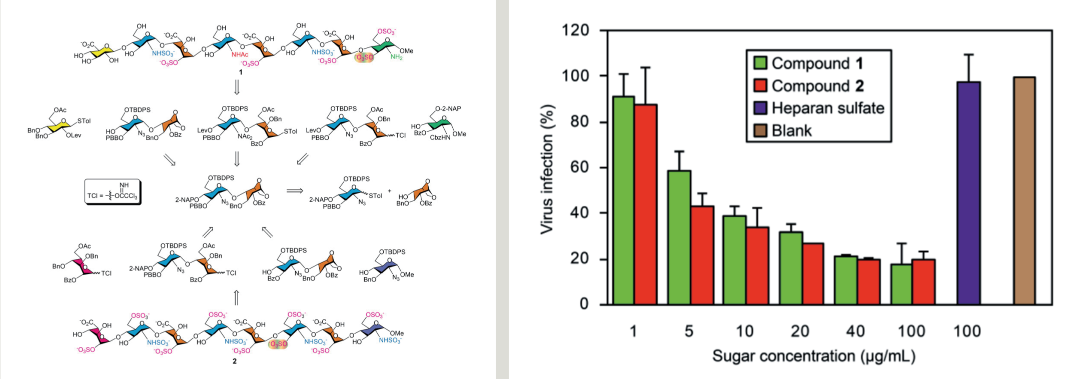
vitro to be a dihydroxylase and a cyclase, respectively. Thirteen high resolution crystal structures for both enzymes in different reaction intermediate states were snapshotted to help elucidate their catalytic mechanisms. OrfP catalyzes an Fe^{II}-dependent double hydroxylation reaction converting L-Arg into (3*R*,4*R*)-$(OH)_2$-L-Arg via (3*S*)-OH-L-Arg, while OrfR catalyzes an unusual PLP-dependent elimination/addition reaction cyclizing (3*R*,4*R*)-$(OH)_2$-L-Arg to the six-membered (4*R*)-OH capreomycidine. The biosynthetic mystery finally comes to light as the latter product was incorporation into STT-F by a feeding experiment.



Biosynthetic conundrum for a hallmark antibiotic solved sheds light on new drug development

- Biosynthesis of streptolidine involved two unexpected intermediates produced by a dihydroxylase and a cyclase through unusual mechanisms. *Angew Chem Int Ed*, 2014, *53*, 1943-8.

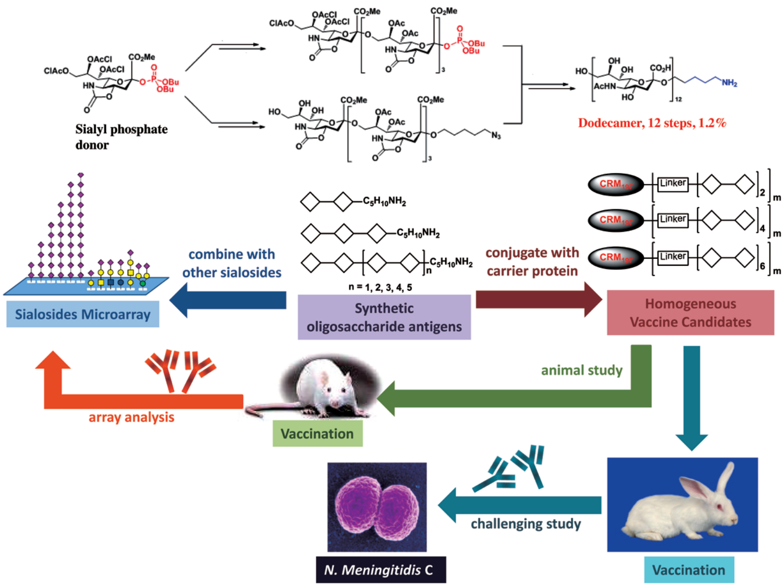
6. Cell surface carbohydrates play significant roles in a number of biologically important processes. Heparan sulfate, for instance, is a ubiquitously distributed polysulfated polysaccharide that is involved, among other things, in the initial step of herpes simplex virus type 1 (HSV-1) infection. The virus interacts with cell-surface heparan sulfate to facilitate host-cell attachment and entry. 3-O-Sulfonated heparan sulfate has been found to function as an HSV-1 entry receptor. Achieving a complete understanding of these interactions requires the chemical synthesis of such oligosaccharides, but this remains challenging. An efficient synthesis of two irregular 3-O-sulfonated heparan sulfate octasaccharides 1 and 2, making use of a key disaccharide intermediate to acquire different building blocks for the oligosaccharide chain assembly, has been carried out by Dr. Hung and his coworkers. Despite substantial structural differences, the prepared 3-O-sulfonated sugars blocked viral infection in a dosage-dependent manner with remarkable similarity to one another.



Inhibition of HSV-1 infection of Vero cells by two octasaccharides

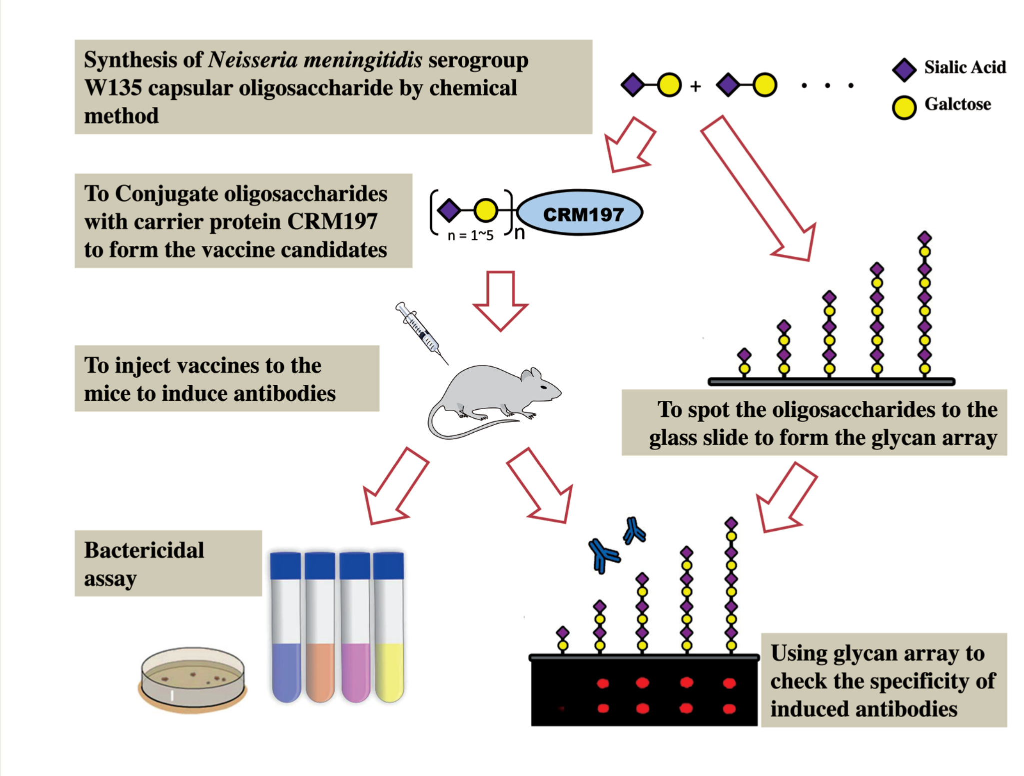
- Synthesis of 3-*O*-sulfonated heparan sulfate octasaccharides that inhibit herpes simplex virus type 1 - host cell interaction. *Nat Chem*, 2011, *3*, 557-63.

7. The linear α(2→9) polysialic acid, which serves as extracellular shield of *Nesseria meningitidis* C against the defense systems of its mammalian host, is considered a good target for the developments of bactericidal agents and antibacterial vaccines. Actually, the vaccines against meningococcal group C diseases have been widely used. However, it is difficult to understand the optimal epitope because the vaccines are constructed by α(2→9) polysialic acids which are isolated from natural sources and often heterogeneous and/or contaminated with other antigenic components. Development of homogeneous *Nesseria meningitidis* C vaccine not only can improve the efficacy and quality control of vaccine, but also help us to understand the optimal epitope. However, high yielding α-selective sialylation is problematic due to the presence of the C-1 electron-withdrawing carboxyl group at the tertiary anomeric center and the lack of a participating group at C-3 to direct the stereochemical outcome of glycosylation. It's particular challenge to synthesize oligosialic acid because the yield and α-selectivity decrease significantly with the increasing of sialyl donor's length. Fortunately, we have overcome these synthetic problems by using a combination of 5-*N*,4-*O*-carbonyl protection and dibutyl phosphate as a reactive leaving group. This sialyl phosphate donor can be successfully applied to convergent block strategy, then different well defined α(2→9) oligosialic acids have been synthesized, including dimer, trimer, tetramer, hexamer, octamer, decamer, and dodecamer. Our synthetic α(2→9) oligosialic acids are useful tools to understand the structure-activity relationships of polysialic acids in various biological events. Finally, we hope to prepare a homogeneous vaccine in order to reduce the risks of impurities in existing heterogeneous vaccine.



Development of homogeneous *Neisseria meningitidis* vaccine via total chemical synthesis

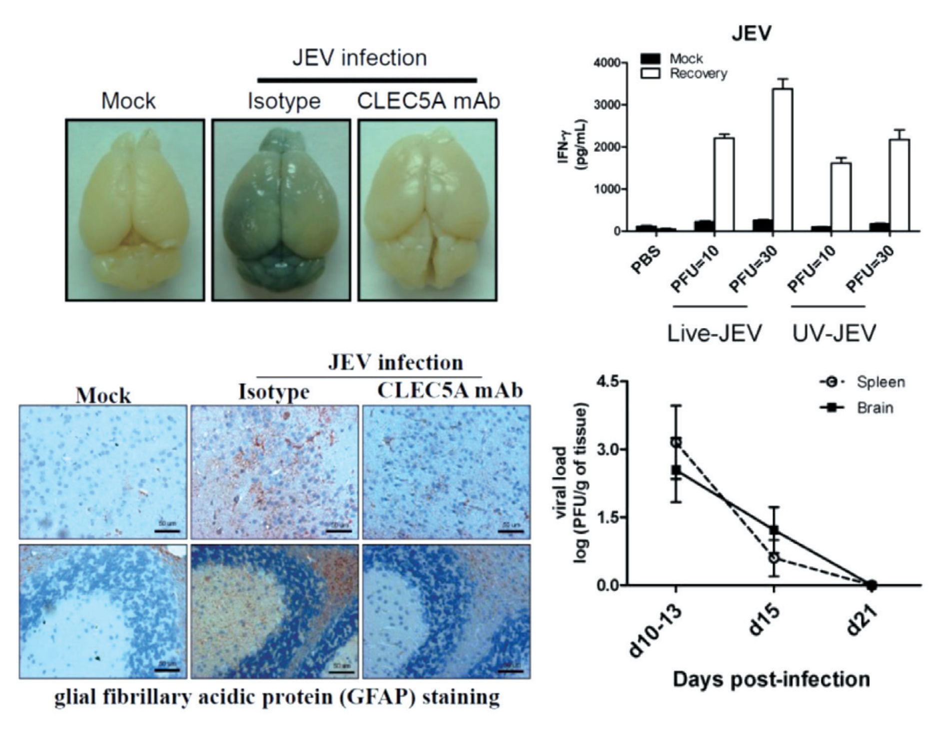
Beside the C type *N. meningitidis*, the research team also synthesized different length of *N. meningitidis* Serogroup W135 capsular sugars and then used them to synthesize vaccines and test them on mouse models and further examined to demonstrate the bactericidal activity of various lengths of sugars, and the results showed that the length as short as tetrasaccharide (with 4 sugars) could sufficiently induce bactericidal activity. The effectiveness of this synthesized vaccine may revolutionize the requirement of high biosafety level for current *N. meningitides* vaccine production, in which the necessary polysaccharides are acquired from pathogenic bacteria and often exist as mixtures of many components. This study also provides a new approach to obtain the necessary polysaccharides by synthesis to create a molecular vaccine that is homogeneous, more consistent, and better quality controlled.



Synthesis of carbohydrate vaccine against *Neisseria meningitidis* serogroup W135

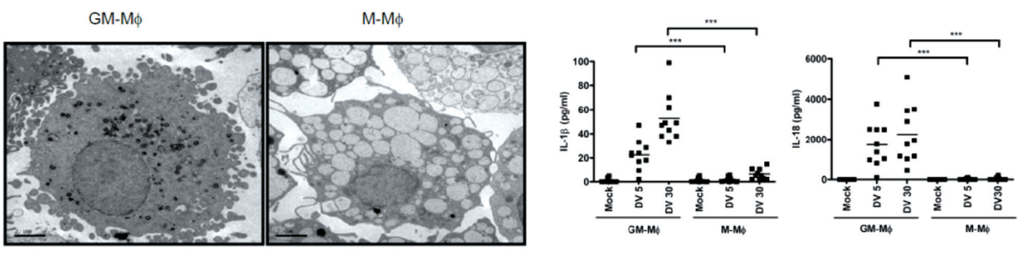
- Efficient and stereoselective synthesis of α(2→9) oligosialic acids: from monomers to dodecamers. *Angew Chem Int Ed*, 2011, *50*, 9391-5.
- Synthesis of capsular oligo-saccharide with various lengths for immunogenicity comparison and vaccine development. *Angew Chem Int Ed*, 2013, *52*, 9157-61.

8. CLEC5A/MDL-1, a member of the myeloid C-type lectin family expressed on macrophages and neutrophils, is critical for dengue virus (DV)-induced hemorrhagic fever and shock syndrome in $Stat1^{-/-}$ mice and ConA-treated wild type mice. However, whether CLEC5A is involved in the pathogenesis of viral encephalitis has not yet been investigated. To investigate the role of CLEC5A to regulate JEV-induced neuroinflammation, antagonistic anti-CLEC5A mAb and CLEC5A-deficient mice were generated. We find that Japanese encephalitis virus (JEV) directly interacts with CLEC5A and induces DAP12 phosphorylation in macrophages. In addition, JEV activates macrophages to secrete proinflammatory cytokines and chemokines, which are dramatically reduced in JEV-infected $Clec5a^{-/-}$ macrophages. Although blockade of CLEC5A cannot inhibit JEV infection of neurons and astrocytes, anti-CLEC5A mAb inhibits JEV-induced proinflammatory cytokine release from microglia and prevents bystander damage to neuronal cells. Moreover, JEV causes blood-brain barrier (BBB) disintegrity and lethality in STAT1-deficient ($Stat1^{-/-}$) mice, whereas peripheral administration of anti-CLEC5A mAb reduces infiltration of virus-harboring leukocytes into the central nervous system (CNS), restores BBB integrity, attenuates neuroinflammation, and protects mice from JEV-induced lethality. Moreover, all surviving mice develop protective humoral and cellular immunity against JEV infection. These observations demonstrate the critical role of CLEC5A in the pathogenesis of Japanese encephalitis, and identify CLEC5A as a target for the development of new treatments to reduce virus-induced brain damage.



Blockade of CLEC5A inhibits JEV-induced neuroinflammation without interfering the activation of adaptive immunity in the survived host

Persistent high fever is one of the most typical clinical symptoms in dengue virus (DV)-infected patients. However, the source of endogenous pyrogen (such as IL-1β) and the signaling cascade leading to the activation of inflammasome and caspase-1, which are essential for IL-1β and IL-18 secretion, during dengue infection have not been elucidated yet. Macrophages can be polarized into distinct phenotypes under the influence of GM-CSF or M-CSF, respectively (denoted as GM-Mφ and M-Mφ). We found that DV induced high levels of IL-1β and IL-18 from GM-Mφ (inflammatory macrophage) and caused cell death (pyroptosis), while M-MΦ (resting macrophage) did not produce IL-1β and IL-18 upon DV infection even with LPS priming. This observation demonstrates the distinct responses of GM-Mφ and M-Mφ to DV infection. Moreover, upregulation of pro-IL-1β, pro-IL-18 and NLRP3 associated with caspase-1 activation was observed in DV-infected GM-Mφ, while blockade of CLEC5A/MDL-1, a C-type lectin critical for dengue hemorrhagic fever (DHF) and Japanese encephalitis virus (JEV) infection, inhibits NLRP3 inflammasome activation and pyroptosis in GM-Mφ. Thus DV can activate NLRP3 inflammasome via CLEC5A, and GM-Mφ play more important roles than M-Mφ in the pathogenesis of DV infection.

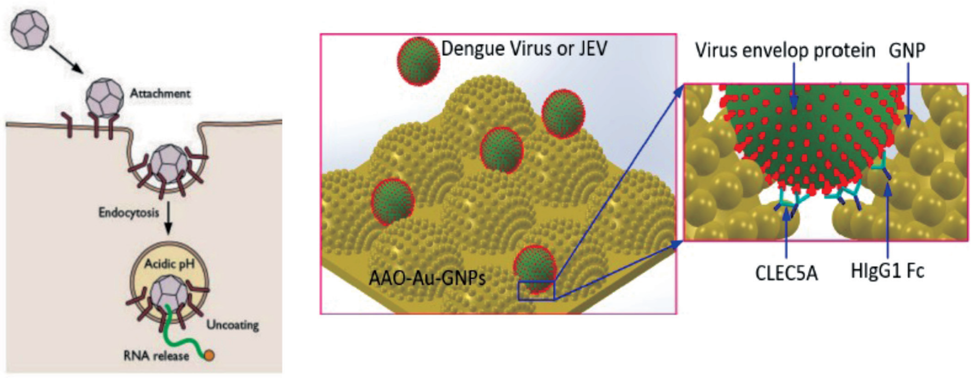


GM-CSF-induced CD14+-macrophages (GM-Mφ or inflammatory macrophages) is the major source of endogenous pyrogens (IL-1β and TNFα) during dengue virus infection

- CLEC5A is critical for dengue-virus-induced lethal disease. *Nature*, 2008, *453,* 672-6.
- CLEC5A regulates Japanese encephalitis virus-induced neuroinflammation and lethality. *PLoS Pathog*. 2012, *8*, e1002655. *FACULTY OF 1000, ƒ1000 Factor 8.0-must read.*
- CLEC5A is critical for dengue virus-induced inflammasome activation in human macrophages. *Blood*, 2013, *121*, 95-106.

9. We develop an effective method for detecting weak molecular bonding between the dengue virus (DV) and its receptor C-type lectin domain family 5, member A (CLEC5A). The CLEC5A-DV interaction is critical for DV-induced hemorrhagic fever and shock syndrome, so the sensing of CLEC5A-DV binding is crucial to realize a thorough study of the pathogenesis of dengue fever. Through a highly sensitive nanostructured sensing electrode of gold nanoparticles (GNPs) uniformly deposited on a nanohemisphere array, a label-free detection of the ultra-weak binding between CLEC5A and the DV can be performed with electrochemical impedance spectroscopy (EIS). Experimental results demonstrate that the proposed approach is a highly promising method for investigating weak molecular interactions such as the ligand-receptor interaction of dengue fever, enterovirus (EV), or the interaction between cancer surface glycoproteins and their receptors (Nanomedicine, doi:10.1016/j.nano.2014.03.009, patent pending).

   In addition, we have used this novel technology to determine the glycosylation sites of dengue virus E proteins bounded by CLEC5A. Based on glycosylation JEV and DV mutants, we found the CLEC5A binds to the second glycosylation site (Asn 153), while DC-SIGN has been reported to bind to first glycosylation site (Asn 67). This result further demonstrates the sensitivity and specificity of this novel technology to determine the ultra-weak binding between lectins and glycans.



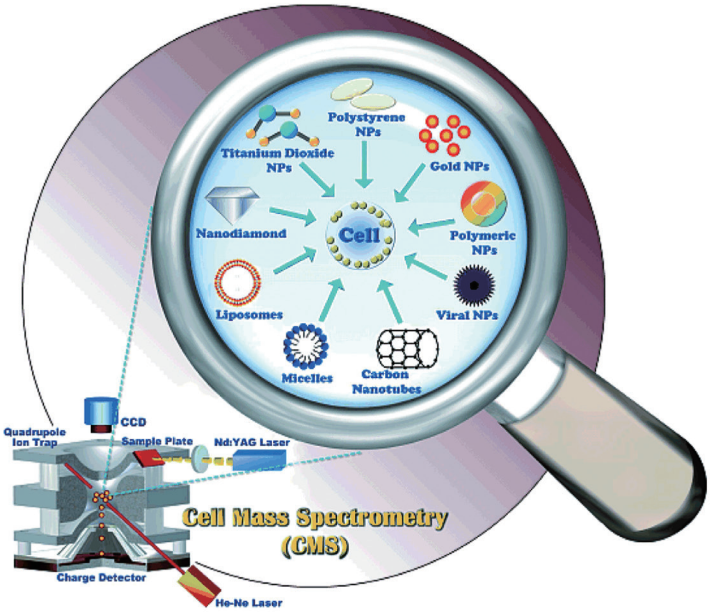
The three dimensional surface contour of the nanohemisphere biosensor mimics the multiple binding site between virus and cell receptor, and dramatically increase the binding avidity between lectin and glycans on the intact virus surface

- Nanostructured electrochemical biosensor for th0065 detection of the weak binding between the dengue virus and the CLEC5A receptor. *Nanomedicine*, 2014, *10*, 1335-41.

Development of novel mass spectrometer for biomedical application

1. Nanoparticle has been considered as an efficient carrier for drug delivery. However, there are no simple methods to measure the uptake of nanoparticle by cells. With the charge-monitoring cell mass spectrometer, we are able to measure the time-resolved uptake of nanoparticles by cells. Up to now, only induction-coupled plasma (ICP) mass spectrometer or emission spectrometer can be used to measure metal nanoparticles. There are still no methods to measure non-metallic nanoparticles uptake by cells. With our charge-monitoring mass spectrometer, both metal and non-metallic particles can be measured.

   Further development led to the first set of measurements of mass and mass distributions for nanoparticles/viruses with rapidity and accuracy. This method can be applied to monitor drug delivery and to measure the degree of infection of viruses in specific cells or in plasma. A label-free quantitative method was also developed for proteome analysis in combination with ID-based Elution time Alignment by Linear regression Quantitation (IDEAL-Q) and MaxQuant. This method has been used to investigate the proteome of liver cancer stem cells and identified unique biomarkers targeting liver cancer stem cells. In addition, a platform was developed based with Raman spectroscopy to monitor the cellular responses to neoplastic drug at a single cell. This strategy is very valuable for rapid and sensitive detection of cellular changes in response to chemotherapeutic agents.

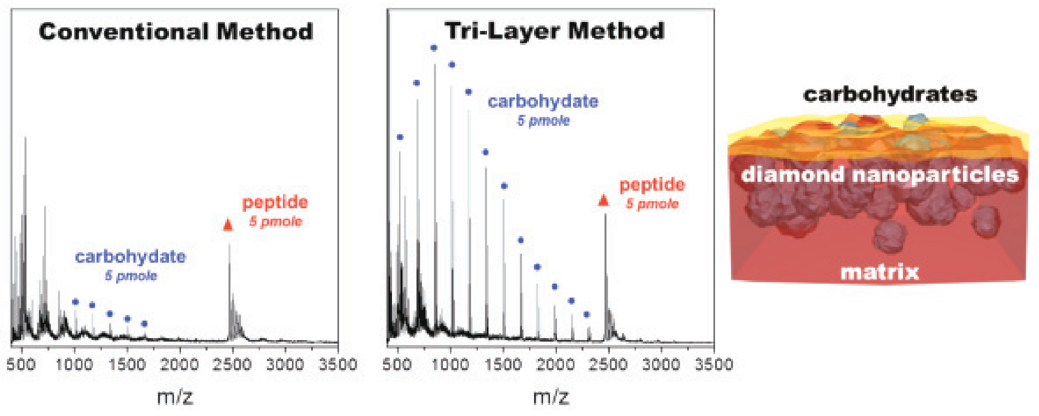


Quantitative measurement of nano/micro particle endocytosis with cell mass spectrometry

- Charge-monitoring laser-induced acoustic desorption mass spectrometry for cell and microparticle mass distribution measurement. *Angew Chem Int Ed*, 2007, *46*, 3865-9.
- Charge monitoring cell mass spectrometry. *Anal Chem*, 2008, *80*, 2524-30.

- Quantitative measurement of nano/micro particle endocytosis with cell mass spectrometry. *Angew Chem Int Ed*, 2010, *49*, 3460-4.
- MALDI ion trap mass spectrometer for quantitative large biomolecular ion detection. *Anal Chem*, 2010, *82*, 10125-8.
- Single nuclei Raman spectroscopy for drug evaluation. *Anal Chem*, 2012, *84*, 113-20.
- High speed mass measurement of nanoparticle and virus. *Anal Chem*, 2012, *84*, 4965-9.
- Label-free quantitative proteomics of CD133-positive liver cancer stem cells. *Proteome Sci*, 2012, *10*, 69.
- Novel mass spectrometry technology development for large organic particle analysis. *RSC Adv,* 2014, *4*, 4523-34.

2. We have focused on the study of detail ionization reaction of biomolecules and developed new methods to improve the sensitivity of mass spectrometer (MS) to carbohydrates. We have demonstrated that the ion production involves multiple pathways because it relies on the sample composition and excitation method. Among the detail reactions, reducing sample temperature and optimizing sample morphology are important to the improvement of the carbohydrate sensitivity. To improve the sample morphology and allow an effective cooling of carbohydrates, we have incorporated diamond nanoparticles into matrix-assisted laser desorption/ionization (MALDI) samples with a tri-layer configuration. The method is convenient and involves no instrumental modification. The excellent thermal, electrical, and optical properties of diamond nanoparticles optimize the ionization condition and improve the sensitivity of MS to underivatized carbohydrates by 1-2 orders of magnitude. Due to the distinct properties of carbohydrates and proteins, this method can selectively enhance the carbohydrate sensitivity from carbohydrate/protein mixtures. In addition to the development of high-performance nanoparticles for carbohydrate identification and quantification, the sample morphology can also be adjusted by controlling the environment for MALDI sample preparation. We have investigated the evolution of the sample distribution with a laboratory-made high spatial resolution synchronized dual-polarity MALDI imaging mass spectrometer. By the precise controlling of substrate temperature, the heterogeneous distribution of typical carbohydrate samples can be reduced to improve the sensitivity and the reproducibility.

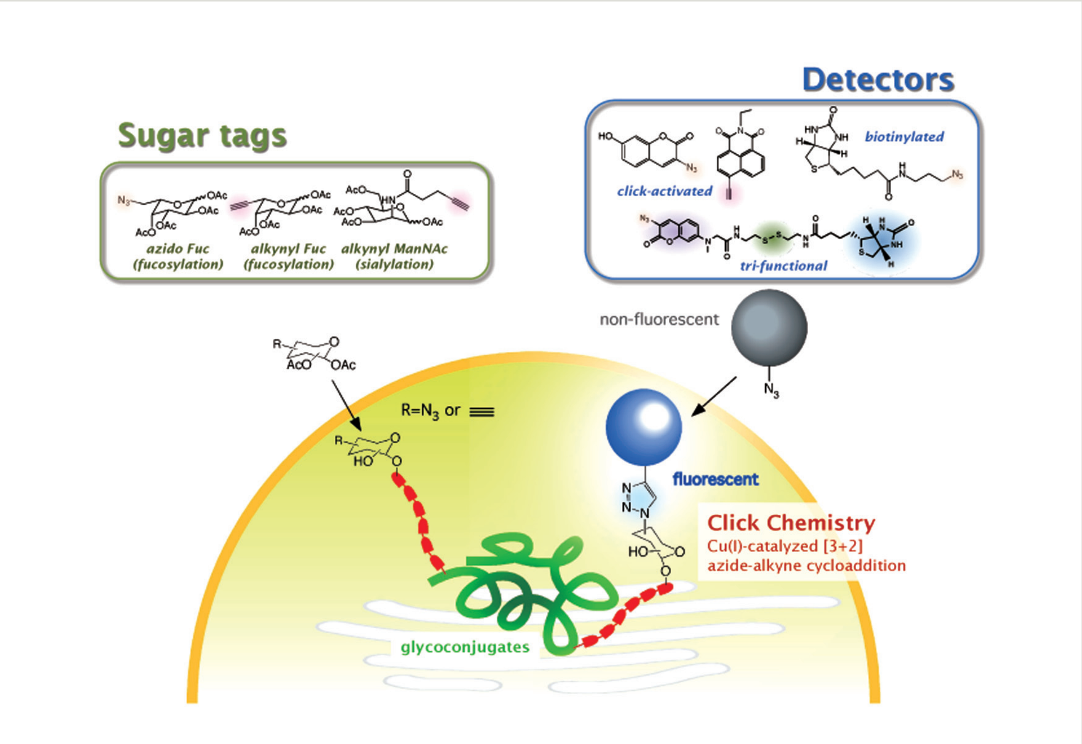


Improved carbohydrate sensitivity by incorporating diamond nanoparticles in samples

- Selective enhancement of carbohydrate ion abundances by diamond nanoparticles for mass spectrometric analysis. *Anal Chem*, 2013, *85,* 3836-41.
- Analysis of initial reactions of MALDI based on chemical properties of matrices and excitation condition. *J Phys Chem B*, 2012, *116*, 9635-43.

Glycan synthesis and development of glycan array for biomedical application

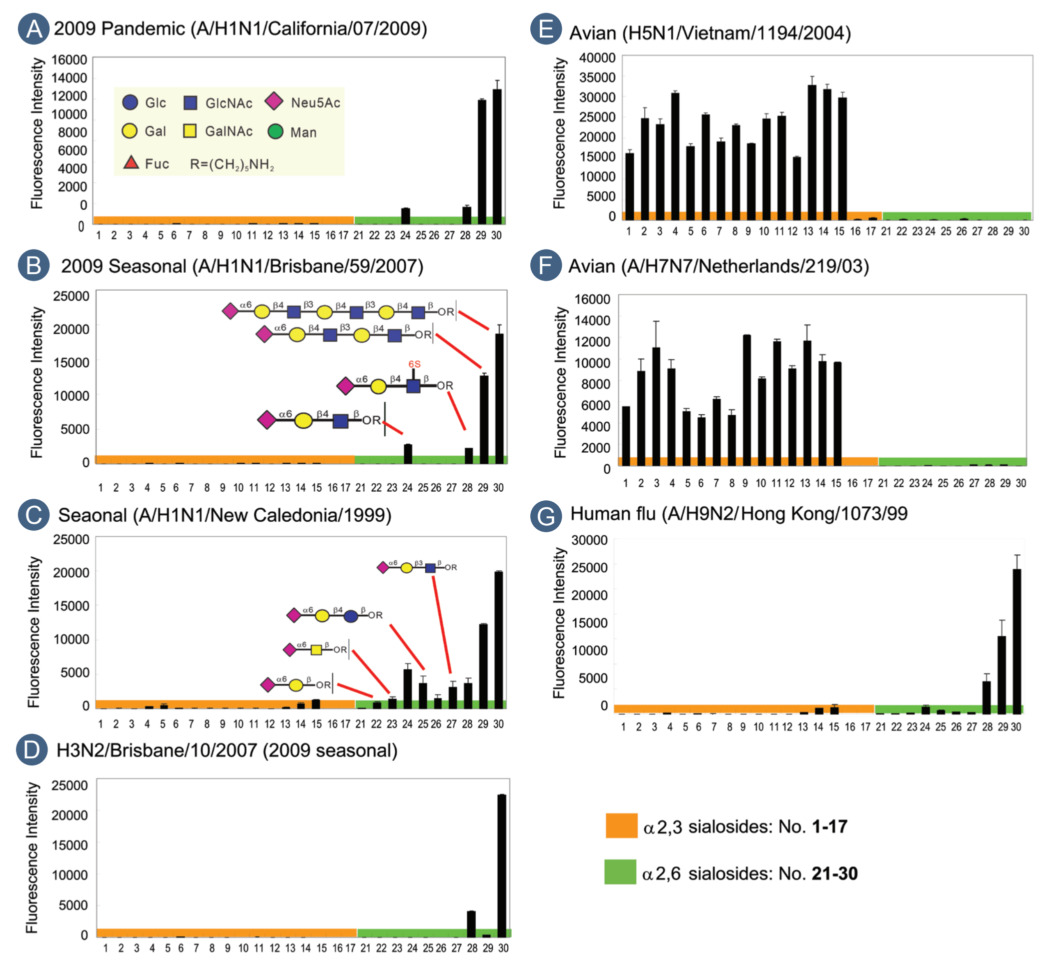
1. Metabolic oligosaccharide engineering, which inserts sugar-reporting groups into cellular glycoconjugates, represents a powerful method for imaging the dynamics of glycans and isolating them for glyco-proteomic analysis. Herein, we show that sugar analogs bearing alkyne-reporting groups can be incorporated into cellular glycans, and chemoselectively labeled by using Cu(I)-catalyzed [3+2] azide-alkyne cycloaddition (Click Chemistry). Our method allows the labeling of fucosyl and sialyl glycoconjugates, which have been shown to associate with cancers. We hope that this tool helps to delineate the molecular basis for aberrant glycosylation in pathological processes, and ultimately leads to diagnostic and therapeutic purposes.



Sugar tags and detectors for probing glycoconjugates in cells

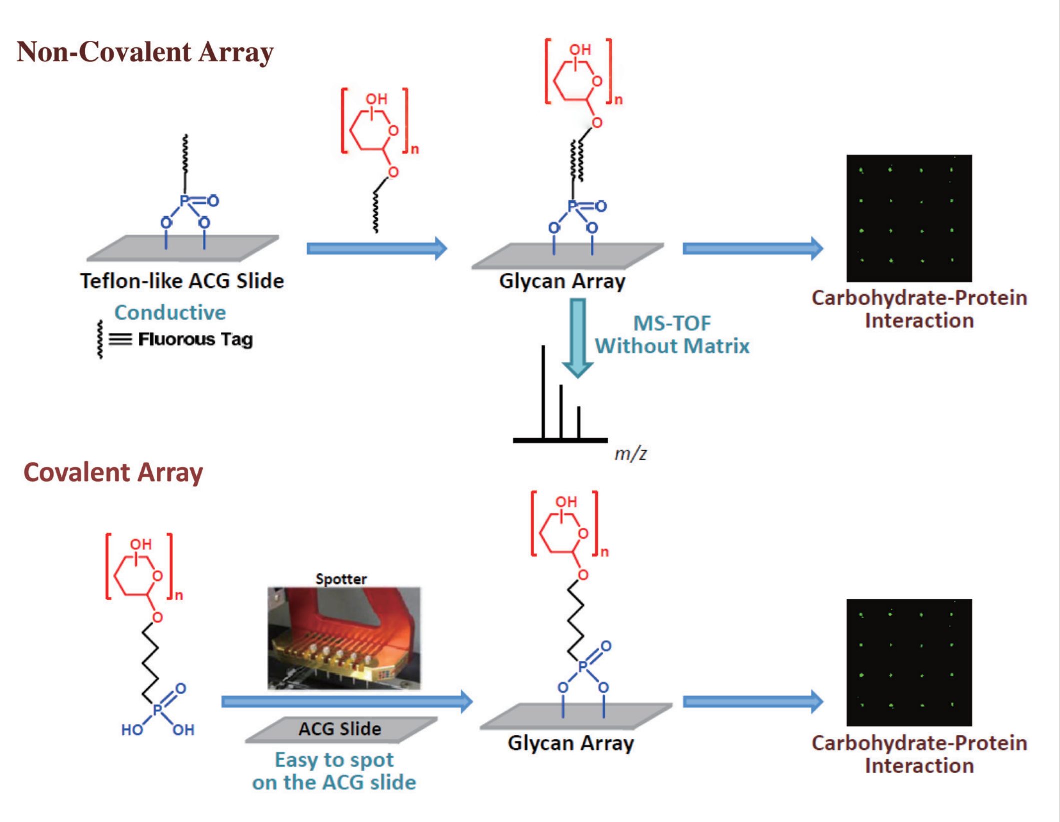
- Glycoproteomic probes for fluorescent imaging of fucosylated glycans in vivo. *Proc Natl Acad Sci USA*, 2006, *103*, 12371-6.
- Alkynyl sugar analogs for the labeling and visualization of glycoconjugates in cells. *Proc Natl Acad Sci USA*, 2007, *104*, 2614-9.
- Tailored glycoproteomics and glycan site mapping using saccharide-selective bioorthogonal probes. *J Am Chem Soc*, 2007, *129*, 7266-7.
- Development of trifunctional probes for glycoproteomic analysis. *Chem Commun (Camb)*, 2010, *46*, 5575-7.

2. Influenza virus infection is initiated by virus attachment to cell-surface sialoside receptors via influenza hemagglutinin (HA). Researchers have developed a new one-pot strategy to synthesize a library of 27 sialosides. By using these 27 sialisides, a glycan array has been constructed and used to profile the binding specificity of different influenza hemagglutinins (HA) subtypes. Analysis of the binding profiles of different HA subtypes indicate that a minimum set of 5 oligosaccharides can be used to differentiate influenza H1, H3, H5, H7 and H9 subtypes. The research result shows, only in a matter of minutes, by applying the infected saliva on the chip, then read by a fluorescence reader, one could pinpoint clearly, if the viral infection is of type A, type B, or a new H1N1 type, or, a rare avian flu that usually only infect birds. So far, a so called "rapid test method" being used in the clinics, can only distinguish if the infection is type A, or, not type A.



Differential binding patterns of HA from H1N1, H3N2, H5N1, H7N7, and H9N2 viruses

Recently, glycan arrays have been developed to mimic their cell-surface display for the study of carbohydrates-receptor interactions and emerged as powerful tools for high-throughput evaluation of interactions between carbohydrates and proteins, cells, and viruses. However, most of glycan arrays used today are difficult to characterize, hard to quantify, and thus lack of quality control. To tackle this problem, research team have recently developed a new type of glycan array covalently or non-covalently attached to aluminum-oxide coated glass (ACG) slides for enzymatic reactions and protein binding studies. To prepare the non-covalent array, glycans with a poly-fluorinated hydrocarbon ($-C_8F_{17}$) tail are spotted robotically onto the ACG slide surface containing a layer of poly-fluorinated hydrocarbon terminated with phosphonate. After incubation and washing, the non-covalent array can be characterized by MS-TOF via ionization/desorption at a low laser energy without addition of matrix. A representative cellotetraose array was developed to study the activity and specificity of various cellulases and to differentiate the exo- and endo-glucanase activities. To prepare the covalent array, glycans with a phosphonic acid tail were synthesized and spotted robotically onto the ACG slide surface. After incubation, the slides can be used directly for quantitative protein binding analysis. Compared to the preparation of glycan arrays on glass slides and other surfaces, this method of arraying using phosphonic acid reacting with ACG is more direct, convenient, effective and represents a new platform for the high-throughput analysis of protein-glycan interactions.



Glycan array on aluminum oxide coated glass slides

- Differential receptor binding affinities of influenza hemagglutinins on glycan arrays. *J Am Chem Soc*, 2010, *132*, 14849-56.
- Glycan array on aluminum oxide coated glass slides through phosphonate chemistry. *J Am Chem Soc*, 2010, 132, 13371-80.

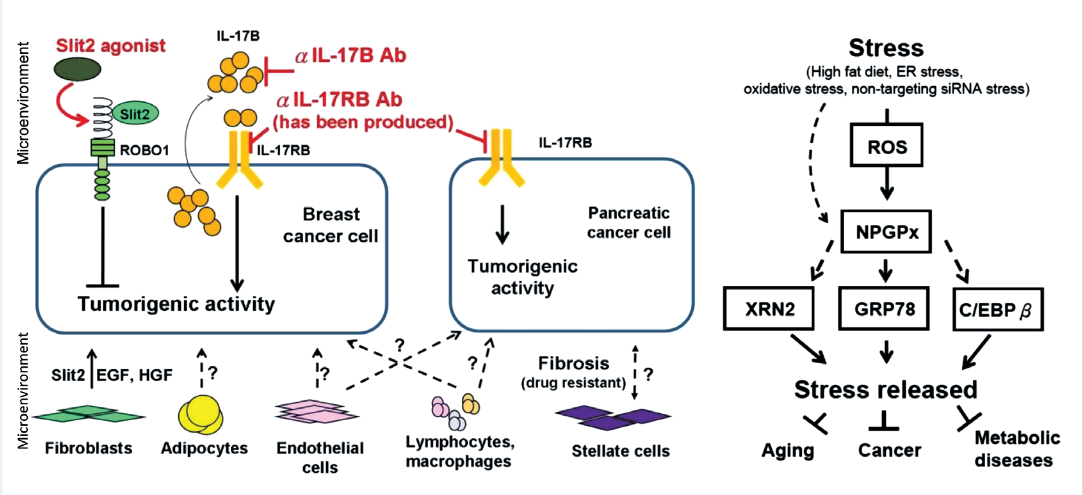
Developing carbonhydrate-based vaccine and immunotherapy for cancer and identifying new insights into tumorigenesis

1. **(A) Microenvironment and tumorigenesis — Elucidation of the interplay between breast / pancreatic cancer cell and its microenvironment.**

   Recently, we are focused in elucidation of the roles of microenvironment in breast and pancreatic tumorigenesis. We identified amplified signaling of interleukin-17 B receptor (IL-17RB) / IL-17B as a novel effector critical for breast as well as pancreatic cancer progression. Conversely, microenvironment restraint of malignant carcinoma progression has been observed. We found that expression of a functional Robo1 receptor in breast cancer cells coupled with Slit2 ligand secretion from stromal fibroblasts inhibited tumorigenesis. Moreover, treatment with effective antibody against IL-17RB blocked tumor metastasis and promoted survival in a mouse xenograft model. These findings illustrate key mechanisms underlying the highly aggressive characteristics of these cancers and provide a practical approach to tackle these diseases (left panel of figure).

   (B) To explore the biological and biochemical functions of NPGPx/GPx7 and its relationship with stress-induced diseases.

   We have demonstrated that NPGPx could sense off-targeting siRNA stress and ER oxidative stress, yield sulfenic acid Cys-SOH of NPGPx, and transfer the stress signal through intermolecular disulfide from NPGPx to target protein including GRP78 and XRN2 and make them activated. The results indicate that NPGPx is important for transmitting stress signals in vivo. Loss of NPGPx induced cancer incidence and metabolic disorder in mice model, indicating that NPGPx is an important target in stress-induced diseases, especially cancer and metabolic disorders. Therefore, the drug screening for metabolic diseases including cancer can be further investigated by using NPGPx KO mice as tool (right panel of figure).

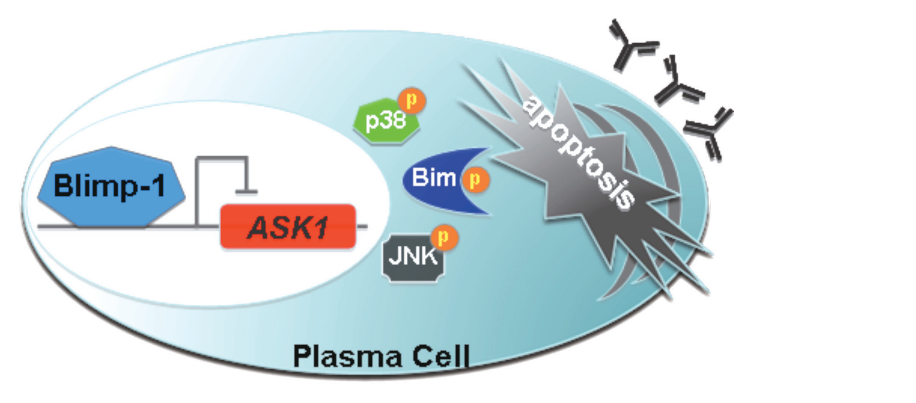


Microenvironment and tumorigenesis / stress and disease

- Activation of Robo1 signaling of breast cancer cells by Slit2 from stromal fibroblast restrains tumorigenesis via blocking Akt/β-catenin pathway. *Cancer Res*, 2012, *72*, 4652-61.
- Loss of the oxidative stress sensor NPGPx compromises GRP78 chaperone activity and induces systemic disease. *Mol Cell*, 2012, *48*, 747-59.

- Deficiency of NPGPx, an oxidative stress sensor, leads to obesity in mice and human. *EMBO Mol Med*, 2013, *5*, 1165-79.
- Autocrine/paracrine mechanism of interleukin-17B receptor promotes breast tumorigenesis through NF-κB-mediated antiapoptotic pathway. *Oncogene*, 2014, *33*, 2968-77.

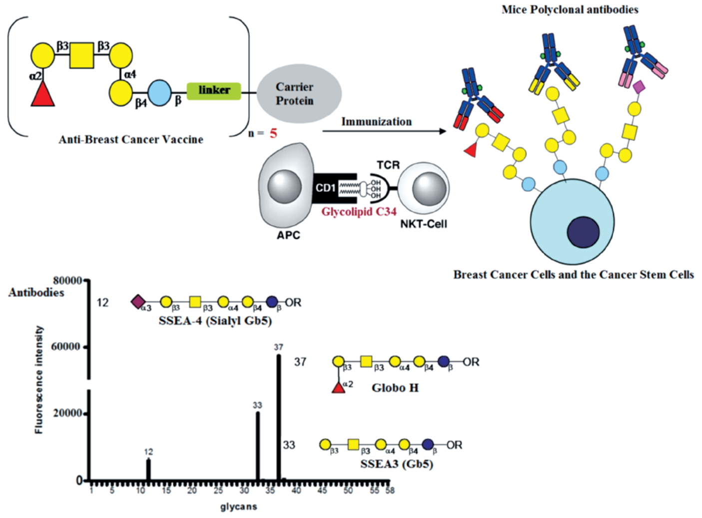
2. Terminally differentiated, antibody-secreting plasma cells are the end-stage effectors of humoral immune responses. Although the overproduction of immunoglobulins by short-lived plasma cells accompanying an immune response links with their apoptosis, how long-lived plasma cells adapt to ensure their longevity in this context is obscure. Dr. Lin's laboratory showed that apoptosis signal-regulating kinase 1 (ASK1) contributes to apoptosis of plasma cells. Antigen-specific long-lived plasma cells generated by immunization accumulated in ASK1-deficient mice. Enforced expression of ASK1 in malignant plasma cells, multiple myeloma (MM), caused apoptosis in vitro and lowered MM load in a xenograft animal model. Additionally, a critical survival-related transcriptional repressor, Blimp-1, is crucial for silencing *ASK1* in maintaining the survival of plasma cells. Their findings not only reveal a novel mechanism underlying the regulation of survival in normal and malignant plasma cells by ASK1 but also provide a new therapeutic insight into plasma cell diseases.



ASK1 regulating apoptosis of normal and malignant plasma cells

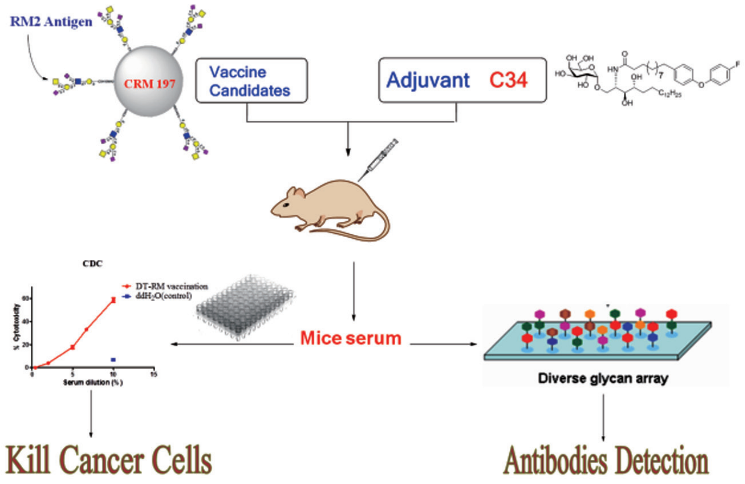
- ASK1 promotes apoptosis of normal and malignant plasma cells. *Blood,* 2012, *120*, 1039-47.

3. Globo H is a potential target for immunotherapy of cancer. Globo H-KLH conjugate combines with adjuvant QS34 is now in phase III clinical trial in Taiwan, and Phase II clinical trial in US, Hong-Kong, Korea, and India for late stage breast cancer patients. However, the antibodies induce by such kind of vaccine is mainly non-memory effect IgM antibodies. We have found that when the hexasaccharide Globo H attached to a diphtheria toxin mutant protein CRM197, DT, in combination with an appropriate adjuvant, such as C34, can efficiently jump-start the immune system and induce abundant IgG antibody to destroy cancer cells. Moreover, the induced antibody specifically recognizes three carbohydrate epitopes, including Globo H, SSEA3 and SSEA4 that only express on breast cancer cells and breast cancer stem cells but not on normal and healthy cells. Compared to the conventional breast cancer target therapy, Herceptin, which is effective for 20% of the breast cancer patients, the Globo H-DT vaccine immunotherapy is expected to be effective for more than 90% of the breast cancer patients and can be developed into a cure or preventive vaccine. The result has been transferred to a biotechnology company in Taiwan for further development.



A carbohydrate vaccine capable of targeting three unique glycan epitopes on breast cancer cells and caner stem cells

We have been studying carbohydrate antigens on the surface of cancer cells and cancer stem cells for many years and found some special carbohydrates. Recently, We detailed the synthesis of a vaccine candidate that induced effective, specific antibodies to eradicate prostate cancer cells in mice. Prostate cancer is the most common cancer for men in developed countries such as the USA. As the fatality rate increases gradually every year, prevention and treatment for the prostate cancer are urgently needed. In 2005, Dr. Hakomori discovered that the amount of RM2 antigen increases as prostate cancer progresses; therefore, RM2 antigen is an excellent biomarker for prostate cancer staging and a good target for developing prostate cancer vaccine. The research team from the GRC is the first ever to successfully synthesize this complex glycan molecule and further attach it to carrier protein CRM197 to create a prostate cancer vaccine candidate, which was combined the previously developed glycolipid adjuvant C34 for vaccine tests in a mice animal model.

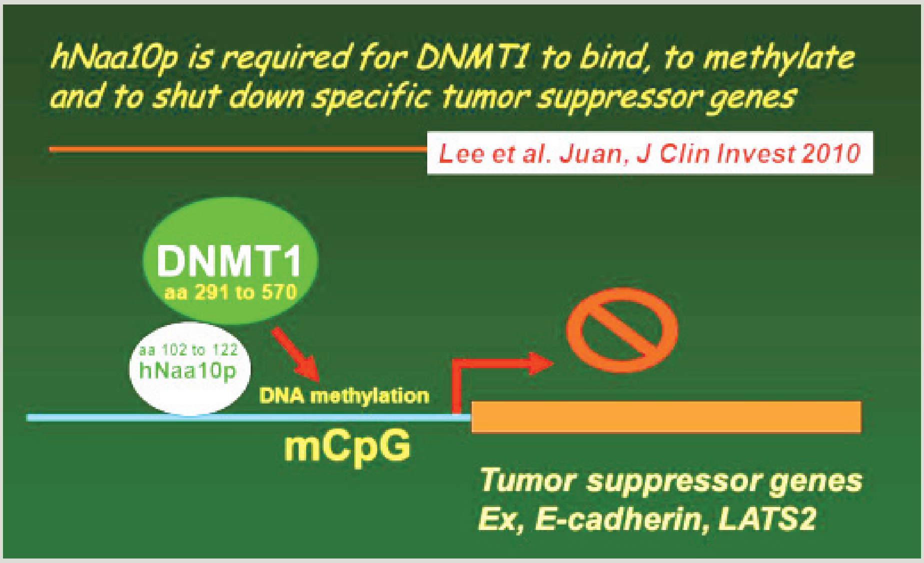


Synthesis and vaccine evaluation of the tumor associated carbohydrate antigen RM2 from prostate cancer

- Potent immune-modulating and anticancer effects of NKT cell stimulatory glycolipids. *Proc Natl Acad Sci USA*, 2007, *104*, 10299-304.

- Expression of Globo H and SSEA3 in breast cancer stem cells and the involvement of fucosyl transferases 1 and 2 in Globo H synthesis. *Proc Natl Acad Sci USA*, 2008, *105*, 11667-72.
- Carbohydrate-based vaccines with a glycolipid adjuvant for breast cancer. *Proc Natl Acad Sci USA*, 2013, *110*, 2517-22.
- Immunization of fucose-containing polysaccharides from Reishi mushroom induces antibodies to tumor-associated Globo H-series epitopes. *Proc Natl Acad Sci USA*, 2013, *110*, 13809-14.
- Synthesis and vaccine evaluation of the tumor-associated carbohydrate antigen RM2 from prostate cancer. *J Am Chem Soc*, 2013, *135*, 11140-50.
- Stage-specific embryonic antigen-4 as a potential therapeutic target in glioblastoma multiforme and other cancers. *Proc Natl Acad Sci USA*, 2014, *111*, 2482-7.

4. Hypermethylation-mediated tumor suppressor gene silencing plays a crucial role in tumorigenesis. Understanding its underlying mechanism is essential for cancer treatment. Previous studies on human N-alpha-acetyltransferase 10, NatA catalytic subunit (hNaa10p; also known as human arrest-defective 1 [hARD1]), have generated conflicting results with regard to its role in tumorigenesis. Here we provide multiple lines of evidence indicating that it is oncogenic. We have shown that hNaa10p overexpression correlated with poor survival of human lung cancer patients. In vitro, enforced expression of hNaa10p was sufficient to cause cellular transformation, and siRNA-mediated depletion of hNaa10p impaired cancer cell proliferation in colony assays and xenograft studies. The oncogenic potential of hNaa10p depended on its interaction with DNA methyltransferase 1 (DNMT1). Mechanistically, hNaa10p positively regulated DNMT1 enzymatic activity by facilitating its binding to DNA in vitro and its recruitment to promoters of tumor suppressor genes, such as E-cadherin, in vivo. Consistent with this, interaction between hNaa10p and DNMT1 was required for E-cadherin silencing through promoter CpG methylation, and E-cadherin repression contributed to the oncogenic effects of hNaa10p. Together, our data not only establish hNaa10p as an oncoprotein, but also reveal that it contributes to oncogenesis through modulation of DNMT1 function.

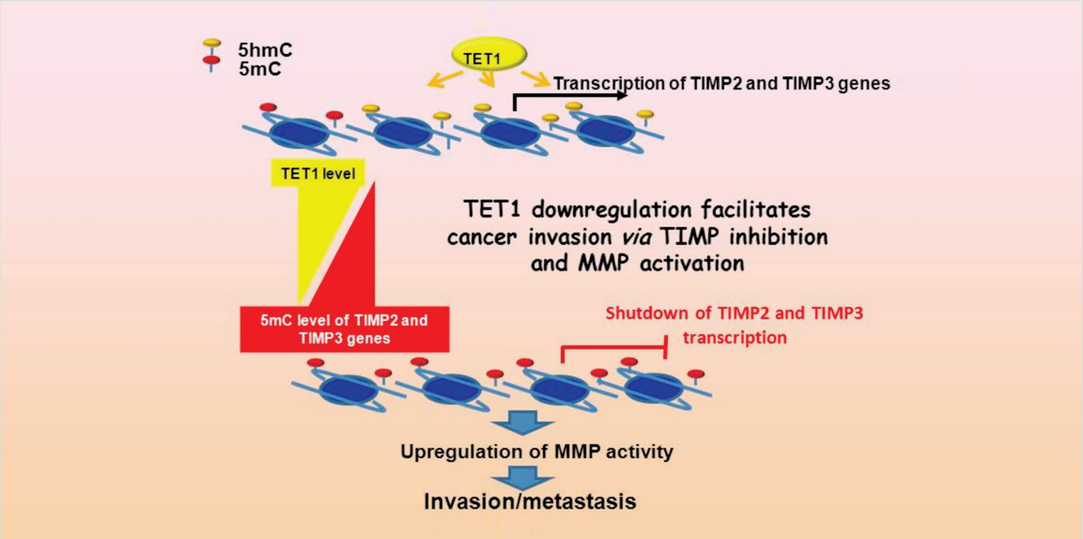


hNaa10p is required for DNMT1 to bind, to methylate and to shut down specific tumor suppressor genes

Lee et al. Juan, J Clin Invest 2010

hNaa10p contributes to tumorigenesis by facilitating DNMT1-mediated tumor suppressor gene silencing

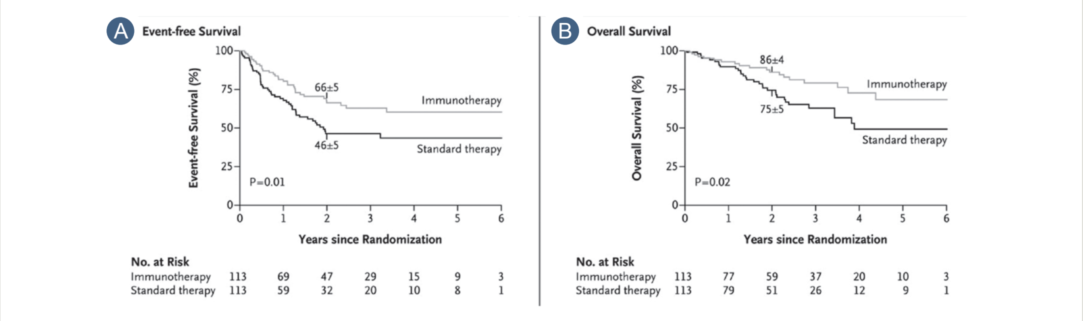
Tumor suppressor gene silencing through cytosine methylation contributes to cancer formation. Whether DNA demethylation enzymes counteract this oncogenic effect is unknown. Here, we showed that TET1, a dioxygenase involved in cytosine demethylation, is downregulated in prostate and breast cancer tissues. TET1 depletion facilitates cell invasion, tumor growth, and cancer metastasis in prostate xenograft models and correlates with poor survival rates in breast cancer patients. Consistently, enforced expression of TET1 reduces cell invasion and breast xenograft tumor formation. Mechanistically, TET1 suppresses cell invasion through its dioxygenase and DNA binding activities. Furthermore, TET1 maintains the expression of tissue inhibitors of metalloproteinase (TIMP) family proteins 2 and 3 by inhibiting their DNA methylation. Concurrent low expression of TET1 and TIMP2 or TIMP3 correlates with advanced node status in clinical samples. Together, these results illustrate a mechanism by which TET1 suppresses tumor development and invasion partly through downregulation of critical gene methylation.



TET1 suppresses cancer invasion via activating the
tissue inhibitors of metalloproteinases

- hNaa10p contributes to tumorigenesis by facilitating DNMT1-mediated tumor suppressor gene silencing. *J Clin Invest*, 2010, *120*, 2920-30.
- TET1 suppresses cancer invasion via activating the tissue inhibitors of metalloproteinases. *Cell Reports*, 2012, *2*, 568-79. *(Best 5 Article of Cell Reports in 2012)*

5. Preclinical and preliminary clinical data indicate that ch14.18, a monoclonal antibody against the tumor-associated disialoganglioside GD2, has activity against neuroblastoma and that such activity is enhanced when ch14.18 is combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) or interleukin-2. We conducted a study to determine whether adding ch14.18, GM-CSF, and interleukin-2 to standard isotretinoin therapy after intensive multimodal therapy would improve outcomes in high-risk neuroblastoma. Immunotherapy with ch14.18, GM-CSF, and interleukin-2 was associated with a significantly improved outcome as compared with standard therapy in patients with high-risk neuroblastoma.



Kaplan–Meier Estimates of Survival among the Study Patients

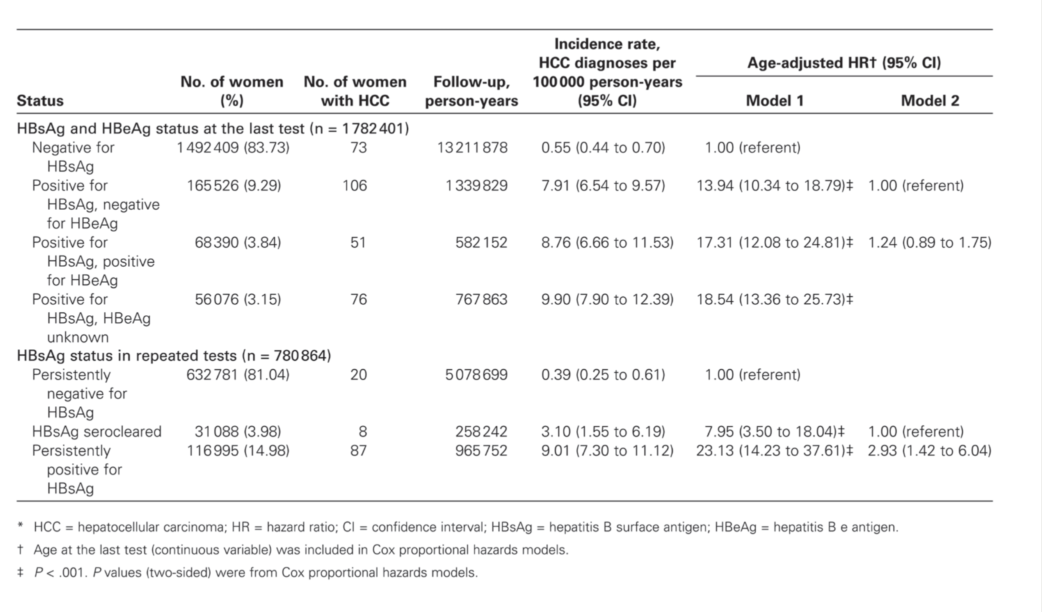
- Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *New Eng J Med*, 2010, *363*, 1324-34.

Implication of hepatitis virus infection and its correlation to development of liver cancer

1. Studies on chronic hepatitis B and hepatocellular carcinoma risk have rarely focused exclusively on women. In this landmark study, a comprehensive nationwide cohort of reproductive-aged Taiwanese women were examined to study the relationship between chronic HBV infection, parity, and hepatocellular carcinoma risk (HCC).

   Using four national registry profiles, data on hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and hepatocellular carcinoma incidence were linked for 1,782,401 women between 1983 and 2000. A total of 306 cases of hepatocellular carcinoma occurred during follow-up. Pregnant women with chronic HBV infection were at much higher risk for HCC; compared to non-infected pregnant women, those with chronic HBV infection had a hazard ratio (95% CI) of developing HCC of 23.13 (14.23-37.61), even after adjustment for age. Especially among women who were born after 1960 and who had live children during follow-up, a positive HBsAg status at their final testing was associated with a hazard ratio (95% CI) of HCC of 14.70 (10.74-20.12). Moreover, compared to women who had one child, women who had two, or three or more children had adjusted hazard ratios of developing HCC of 0.68 (0.50-0.93) and 0.63 (0.42-0.92), respectively.

   This study found that women with chronic HBV infection had a higher risk for developing hepatocellular carcinoma, compared to women who were not infected. Interestingly, the risk for HCC decreased as parity increased, independent of HBsAg status and age. The exact mechanisms underlying the association between parity and reduced HCC risk should be further investigated.



Status	No. of women (%)	No. of women with HCC	Follow-up, person-years	Incidence rate, HCC diagnoses per 100 000 person-years (95% CI)	Age-adjusted HR† (95% CI)	
					Model 1	Model 2
HBsAg and HBeAg status at the last test (n = 1 782 401)						
Negative for HBsAg	1 492 409 (83.73)	73	13 211 878	0.55 (0.44 to 0.70)	1.00 (referent)	
Positive for HBsAg, negative for HBeAg	165 526 (9.29)	106	1 339 829	7.91 (6.54 to 9.57)	13.94 (10.34 to 18.79)‡	1.00 (referent)
Positive for HBsAg, positive for HBeAg	68 390 (3.84)	51	582 152	8.76 (6.66 to 11.53)	17.31 (12.08 to 24.81)‡	1.24 (0.89 to 1.75)
Positive for HBsAg, HBeAg unknown	56 076 (3.15)	76	767 863	9.90 (7.90 to 12.39)	18.54 (13.36 to 25.73)‡	
HBsAg status in repeated tests (n = 780 864)						
Persistently negative for HBsAg	632 781 (81.04)	20	5 078 699	0.39 (0.25 to 0.61)	1.00 (referent)	
HBsAg serocleared	31 088 (3.98)	8	258 242	3.10 (1.55 to 6.19)	7.95 (3.50 to 18.04)‡	1.00 (referent)
Persistently positive for HBsAg	116 995 (14.98)	87	965 752	9.01 (7.30 to 11.12)	23.13 (14.23 to 37.61)‡	2.93 (1.42 to 6.04)

* HCC = hepatocellular carcinoma; HR = hazard ratio; CI = confidence interval; HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen.

† Age at the last test (continuous variable) was included in Cox proportional hazards models.

‡ *P* < .001. *P* values (two-sided) were from Cox proportional hazards models.

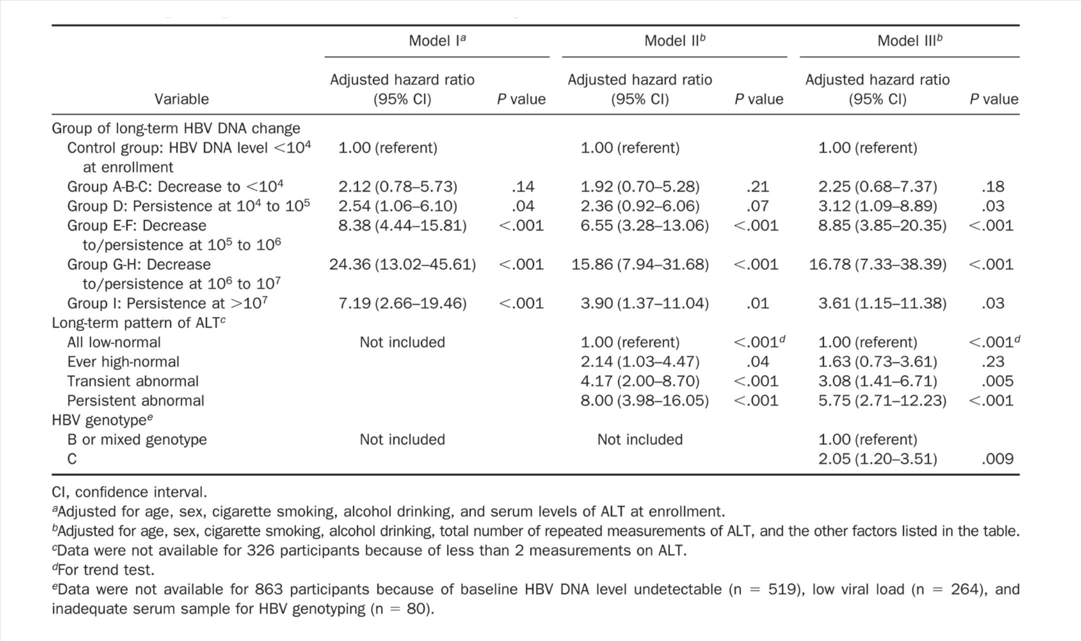
Incidence of hepatocellular carcinoma during follow-up and the association of hepatitis B virus status with risk of hepatocellular carcinoma

- Role of reproductive factors in hepatocellular carcinoma: impact on hepatitis B- and C-related risk. *Hepatology*, 2003, *38*, 1393-1400.
- Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*, 2006, *295*, 65-73.
- Hepatitis B virus infection and hepatocellular carcinoma among parous Taiwanese women: Nationwide cohort study. *J Natl Cancer Inst*, 2009, *101*, 1019-27.

2. Studies on the association between long-term trajectories of HBV DNA and ALT are still incomplete. In this study, a large cohort of individuals infected with chronic hepatitis B were followed-up with repeated measurements of HBV DNA and ALT for an average of 12 years, and data from repeated measurements was used to determine long term trajectories.

   In this study 3160 individuals were followed-up for a total of 38,330 person-years, during which 81 participants developed incident hepatocellular carcinoma (HCC). A total of six different long-term trajectories of HBV DNA were determined from long-term follow-up data using the group-based trajectory method, while ALT was classified into four patterns. Compared with the control group of individuals with baseline HBV DNA levels <10,000 copies/mL, the HRs (95% CI) for long-term levels of HBV DNA that persisted at 10,000 to 100,000 copies/mL, decreased to/persisted at 100,000 to 1,000,000 copies/mL, or decreased to/persisted at 1,000,000 to 10,000,000 copies/mL were 3.12 (1.09-8.89), 8.85 (3.85-20.35), and 16.78 (7.33-38.39), respectively. A gradient in ALT level was significantly associated with hepatocellular carcinoma risk: from all low-normal, to ever high-normal, to transient abnormal, to persistent abnormal (*P*trend = .001).

   This study found that long-term HBV DNA changes are strong independent risk predictors of HCC; even in individuals with similar HBV DNA levels at study entry, their future HCC risk varied greatly depending on their changes during follow-up. Greater decreases in serum HBV DNA levels were associated with lower risks of HCC. Regular monitoring of HBV DNA and ALT levels is crucial during clinical management of chronic HBV carriers.



Variable	Model I[a]		Model II[b]		Model III[b]	
	Adjusted hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Group of long-term HBV DNA change						
Control group: HBV DNA level $<10^4$ at enrollment	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Group A-B-C: Decrease to $<10^4$	2.12 (0.78–5.73)	.14	1.92 (0.70–5.28)	.21	2.25 (0.68–7.37)	.18
Group D: Persistence at 10^4 to 10^5	2.54 (1.06–6.10)	.04	2.36 (0.92–6.06)	.07	3.12 (1.09–8.89)	.03
Group E-F: Decrease to/persistence at 10^5 to 10^6	8.38 (4.44–15.81)	<.001	6.55 (3.28–13.06)	<.001	8.85 (3.85–20.35)	<.001
Group G-H: Decrease to/persistence at 10^6 to 10^7	24.36 (13.02–45.61)	<.001	15.86 (7.94–31.68)	<.001	16.78 (7.33–38.39)	<.001
Group I: Persistence at $>10^7$	7.19 (2.66–19.46)	<.001	3.90 (1.37–11.04)	.01	3.61 (1.15–11.38)	.03
Long-term pattern of ALT[c]						
All low-normal	Not included		1.00 (referent)	<.001[d]	1.00 (referent)	<.001[d]
Ever high-normal			2.14 (1.03–4.47)	.04	1.63 (0.73–3.61)	.23
Transient abnormal			4.17 (2.00–8.70)	<.001	3.08 (1.41–6.71)	.005
Persistent abnormal			8.00 (3.98–16.05)	<.001	5.75 (2.71–12.23)	<.001
HBV genotype[e]						
B or mixed genotype	Not included		Not included		1.00 (referent)	
C					2.05 (1.20–3.51)	.009

CI, confidence interval.

[a] Adjusted for age, sex, cigarette smoking, alcohol drinking, and serum levels of ALT at enrollment.

[b] Adjusted for age, sex, cigarette smoking, alcohol drinking, total number of repeated measurements of ALT, and the other factors listed in the table.

[c] Data were not available for 326 participants because of less than 2 measurements on ALT.

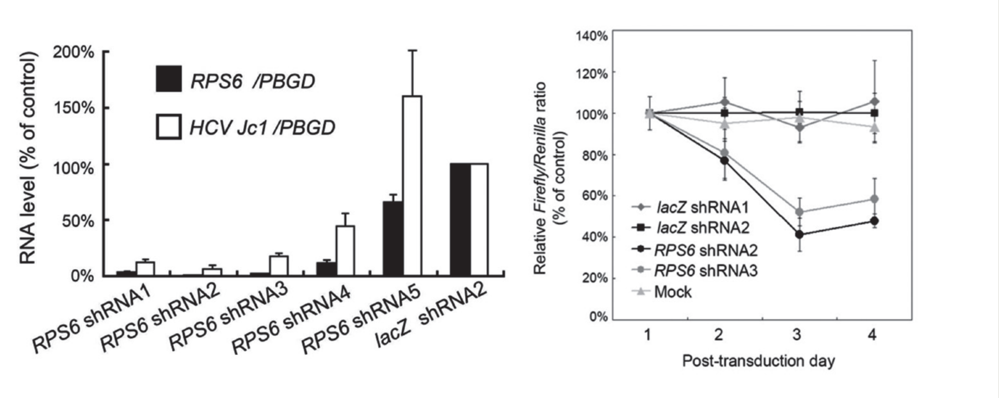
[d] For trend test.

[e] Data were not available for 863 participants because of baseline HBV DNA level undetectable (n = 519), low viral load (n = 264), and inadequate serum sample for HBV genotyping (n = 80).

Multivariate-adjusted hazard ratio of developing hepatocellular carcinoma for group of long-term HBV DNA change, long-term pattern of ALT, and HBV genotype

- Epidemiological characteristics and risk factors of hepatocellular carcinoma. *J Gastroenterol Hepatol*, 1997, *12*, S294-308.
- Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*, 2006, *295*, 65-73.
- Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. *Hepatology*, 2009, *49*, S72-84.
- Changes in serum levels of HBV DNA and alanine aminotransferase determine risk for hepatocellular carcinoma. *Gastroenterology*, 2011, *141*, 1240-8.

3. Chronic hepatitis C virus (HCV) infection is an epidemic viral disease that threatens ~3% of the world population and is a major cause of hepatic cirrhosis, liver failure, and hepatocellular carcinoma. Current standard therapy is only effective for <50% of genotype-1- and ~80% of genotypes 2 and 3-infected patients. Conventional drug designs often target viral proteins, which invariably result in drug resistance due to rapid viral mutations. An alternative strategy is to explore the genetic stability of host factors that are essential for HCV replication. To this end, we employed the RNAi technology to search for such critical host-cell components and unexpectedly found that HCV replication can be effectively repressed by attenuating the 40S-ribosomal-subunit abundance without negatively impacting on the host vitality. This finding thus opens up a new avenue for developing anti-HCV therapeutics. Because ribosomal 40S subunit has been perfected over millions of years of evolution, it is extremely unlikely to morph or mutate as freely as viruses. Thus, finding a good way to fine-tune the 40S ribosomal subunit level as part of the HCV therapeutics may not only be feasible, but also superior in terms of minimizing drug-resistance problem and maintaining the drug shelf life.

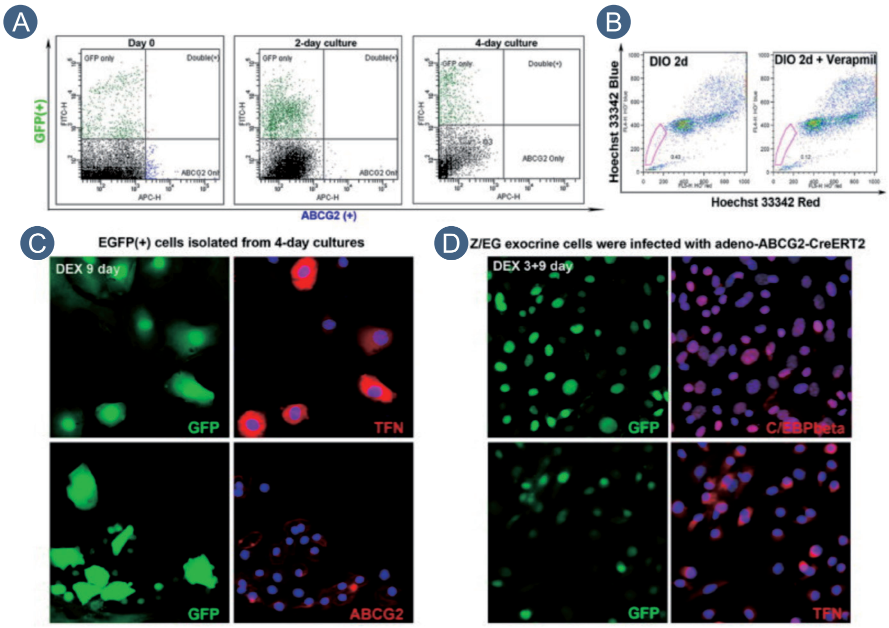


Attenuation of 40S ribosomal subunit abundance specifically represses HCV replication via preferentially shut down of HCV RNA translation

- Attenuation of 40S ribosomal subunit abundance differentially affects host and HCV translation and suppresses HCV replication. *PLoS Pathog*, 2012, *8*, e1002766.

Stem cell discovery for regenerative medicine

1. The appearance of hepatocytes in adult pancreas is one example of transdifferentiation that has been observed in cancer patients. However, the mechanism underlying the pancreatic-to-hepatic conversion is less clear. The current study revealed that hepatocytes were derived from differentiated acinar cells via ABCG2-expressing intermediates. Exposure of acinar cells to glucocorticoids together with insulin increased Akt phosphorylation, ABCG2 expression, and hepatic transdifferentiation. When ABCG2-expressing cells were incubated with glucagon-like-peptide 1, these cells could differentiate into insulin-producing beta cells suggesting ABCG2-expressing cells resemble adult pancreatic multipotent stem/progenitor cells. The current findings imply donor pancreatic exocrine cells can be utilized to generate multipotent cells, insulin-producing beta cells or functional hepatocytes which may lead to development of new therapeutic strategies for patients with diabetes or acute liver failure.

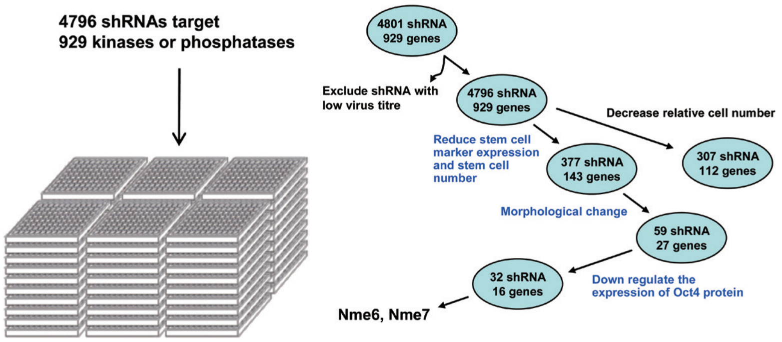


Direct transdifferentiation of adult mouse pancreatic acinar cells to hepatocytes and ABCG2-positive intermediates

- Differentiation of pancreatic acinar cells to hepatocytes requires an intermediate cell type. *Gastroenterology*, 2010, *138*, 2519-30.

2. In contrast to the somatic cells, embryonic stem cells (ESCs) are characterized by its immortalization ability, pluripotency, and oncogenicity. Revealing the underlying mechanism of ESC characteristics is important for the application of ESCs in clinical medicine. We performed the first systematic functional shRNA screen in mouse ESCs with 4,801 shRNAs that target 929 kinases and phosphatases. This screen can identify both positive/negative regulators and is the first shRNA high throughput screen in ESCs. 132 candidate genes that regulate both ESC expansion and stem cell marker expression were identified. Twenty-seven out of the 132 genes were regarded as most important since knockdown of each gene induces morphological changes from undifferentiated to differentiated state. Among the 27 genes, we chose nonmetastatic cell 6 (Nme6, Nm23-H6) and nonmetastatic cell 7 (Nme7, Nm23-H7) to study first. Nme6 and Nme7 both belong to the members of nucleoside diphosphate kinase family. We demonstrate that Nme6 and Nme7 are important for the regulation of Oct4, Nanog, Klf4, c-Myc, telomerase, Dnmt3B, Sox2, and ERas expression. Either knockdown of Nme6 or Nme7

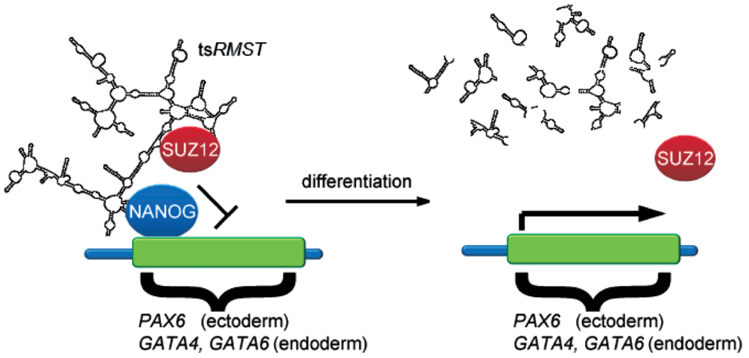
reduces the formation of embryoid body (EB) and teratoma. The overexpression of either Nme6 or Nme7 can rescue the stem cell marker expression and the EB formation in the absence of leukemia inhibiting factor. This implies the importance of Nme6 and Nme7 in ESC renewal. This finding not only pinpoints Nme6 or Nme7 can regulate several critical regulators in ESC renewal but also increases our understanding of the ESC renewal and oncogenesis.



A systematically high throughput screen in mouse ESCs

- A shRNA functional screen reveals Nme6 and Nme7 are crucial for embryonic stem cell renewal. *Stem Cells*, 2012, *30*, 2199-211.
- Array-based high throughput screen in mouse embryonic stem cells with shRNAs. *Curr Protoc Stem Cell Biol*, 2013, *26*, 5C.3.1-5C.3.19.

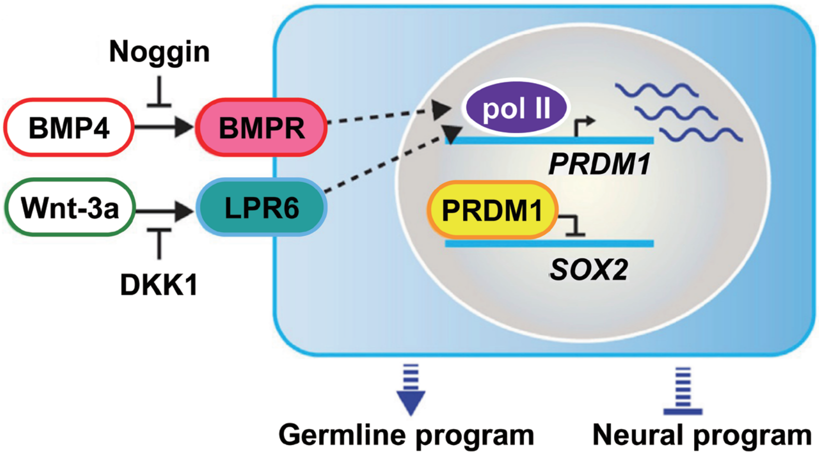
3. Trans-splicing is a post-transcriptional event that joins exons from separate pre-mRNAs. Detection of trans-splicing is usually severely hampered by experimental artifacts and genetic rearrangements. Here, we develop a new computational pipeline, TSscan, which integrates different types of high-throughput long-/short-read transcriptome sequencing of different human embryonic stem cell (hESC) lines to effectively minimize false positives while detecting trans-splicing. Combining TSscan screening with multiple experimental validation steps revealed that most chimeric RNA products were platform-dependent experimental artifacts of RNA sequencing. We successfully identified and confirmed four trans-spliced RNAs, including the first reported trans-spliced large intergenic noncoding RNA ("tsRMST"). We showed that these trans-spliced RNAs were all highly expressed in human pluripotent stem cells and differentially expressed during hESC differentiation. Our results further indicated that tsRMST can contribute to pluripotency maintenance of hESCs by suppressing lineage-specific gene expression through the recruitment of NANOG and the PRC2 complex factor, SUZ12. Taken together, our findings provide important insights into the role of trans-splicing in pluripotency maintenance of hESCs and help to facilitate future studies into trans-splicing, opening up this important but understudied class of post-transcriptional events for comprehensive characterization.



A putative model for regulation of gene expression by tsRMST in pluripotent stem cells

- Integrative transcriptome sequencing identifies trans-splicing events with important roles in human embryonic stem cell pluripotency. *Genome Res*, 2014, *24*, 25-36.

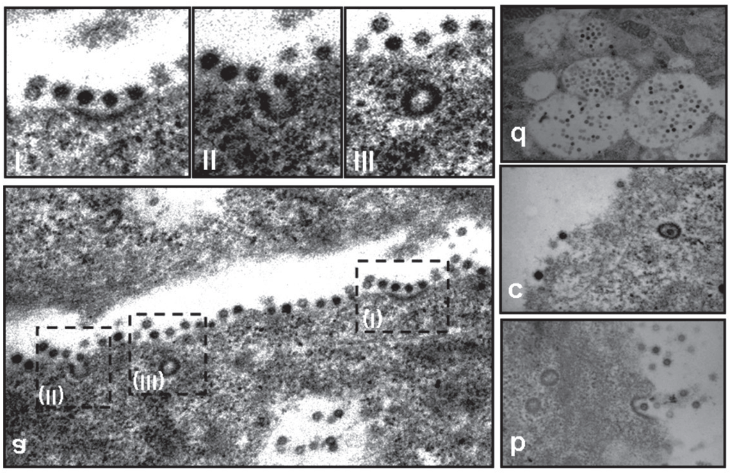
4. The mechanisms of transcriptional regulation underlying human primordial germ cell (PGC) differentiation are largely unknown. The transcriptional repressor Prdm1/Blimp-1 is known to play a critical role in controlling germ cell specification in mice. Here, Dr. Lin's group showed that PRDM1 is expressed in developing human gonads and contributes to the determination of germline versus neural fate in early development. They showed that knockdown of PRDM1 in human embryonic stem cells (hESCs) impairs germline potential and upregulates neural genes. Conversely, ectopic expression of PRDM1 in hESCs promotes the generation of cells that exhibit phenotypic and transcriptomic features of early PGCs. Furthermore, PRDM1 suppresses transcription of SOX2. Overexpression of SOX2 in hESCs under conditions favoring germline differentiation skews cell fate from the germline to the neural lineage. Collectively, their results demonstrate that PRDM1 serves as a molecular switch to modulate the divergence of neural or germline fates through repression of SOX2 during human development.



A Working model of the function of PRDM1 in germline differentiation by hESCs

- Suppression of the SOX2 neural effector gene by PRDM1 promotes human germ cell fate in embryonic stem cells. *Stem Cell Reports*, 2014, *2*, 189-204.

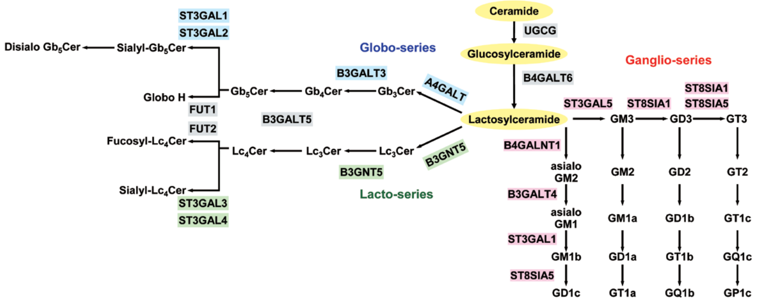
5. The team led by Dr. John Yu had identified a rare and primitive subpopulation of pulmonary cells that correspond to slow cycling, Oct-4$^+$ expressing cells scattering at bronchoalveolar junctions of lung tissues, and exhibit the characteristics of pulmonary stem/progenitor cells. In addition to Oct-4, these cells also expressed other stem cell markers such as Nanog, SSEA-1, and Sca-1, but not c-Kit, CD34 or p63. Recently, these clonogenic cells have been further purified by selective markers (e.g. CXCR4, ABCG2, etc.) and specific culture conditions to promote substantially greater number and size of large colonies. We have also demonstrated that pulmonary stem cells are preferentially infected by SARS-CoV. The infection of stem cells by the newly evolved viruses may lead to loss of capacity for lung repair and serious lung failure.



SARS-CoV infects pulmonary stem cells showing the active replication of viruses

- Identification of pulmonary Oct-4^+ stem/progenitor cells and demonstration of their susceptibility to SARS coronavirus (SARS-CoV) infection in vitro. *Proc Natl Acad Sci USA*, 2006, *103*, 9530-5.

6. Systematic surveys of expression profiles of glycosphingolipids (GSLs) in the undifferentiated hESC lines, their differentiated embryoid body (EB) outgrowth cells, and further differentiated neural progenitors or definitive endodermal cells were carried out using MALDI-MS and MS/MS analyses. During hESC differentiation into EBs, a clear-cut switch in the core structures of GSLs from globo- and lacto- to ganglio-series. During hESC differentiation into neural progenitor cells, a similar switch of GSLs was observed, which is dominated by GD3. On the other hand, when hESCs were differentiated into endodermal cells, patterns of GSLs totally differed from those observed in EB outgrowth and neural progenitors. The most prominent GSL was Gb_4Ceramide, with no appreciable amount of stage-specific embryonic antigens 3 or 4, or GD3, in endodermal cells. These changes in GSL profiling were accompanied by alterations in the biosynthetic pathways of expressions of key glycosyltransferases. The findings suggest that changes in GSLs are closely associated with lineage specificity and differentiation of hESCs. These results provide insights into the unique stage-specific transition and mechanism for alterations of GSL core structures during hESC differentiation. Since the specific hESC markers may also be found in cancers, the unique glycan structures uncovered in this study may serve as surface markers for further delineation of hESCs and help identification of their functional roles not only in hESCs but also in cancers.

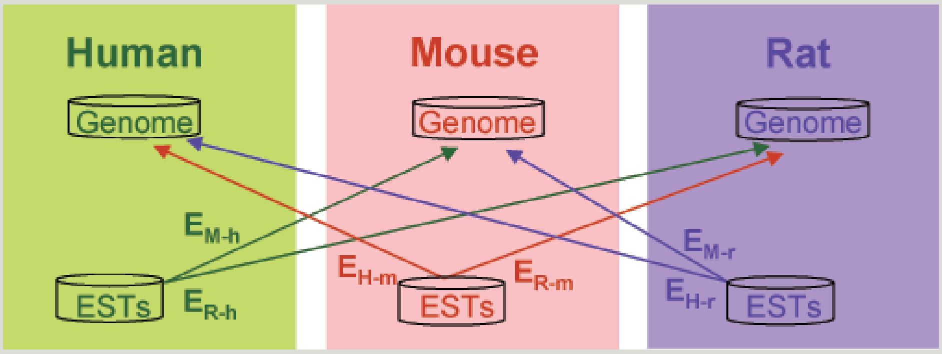


The biosynthesis of glycosphingolipids and the key glycosyltransferases involved during hESC differentiation

- Switching of the core structures of glycosphingolipids from globo- and lacto- to ganglio-series upon human embryonic stem cell differentiation. *Proc Natl Acad Sci USA*, 2010, *107*, 22564-9.
- Changes in glycosphingolipid composition during differentiation of human embryonic stem cells to ectodermal or endodermal lineages. *Stem Cells*, 2011, *29*, 1995-2004.

Determining genome structure and identifying genetic insights of diseases

1. We have developed several comparative algorithms, including PSEP, ENACE, and PGAA, for identification of gene structures or alternatively spliced variants (ASVs) on the basis of cross-species EST-to-genome and genome-to-genome comparisons. These methods are not only suitable for identifying previously uncharacterized exons/ASVs but also for studying the evolution of ASVs. Especially, we demonstrated that ENACE is very useful for identifying novel exons/ASVs for EST-scanty species by applying rich EST data from a closely related species. We also designed two Web interface (ESTviewer and RiceViewer) for interactively visualizing, respectively, human and rice gene structures/ASVs.



The concept of the ENACE annotator. Arrows indicate mapping of ESTs from the source species to the genome of the target species

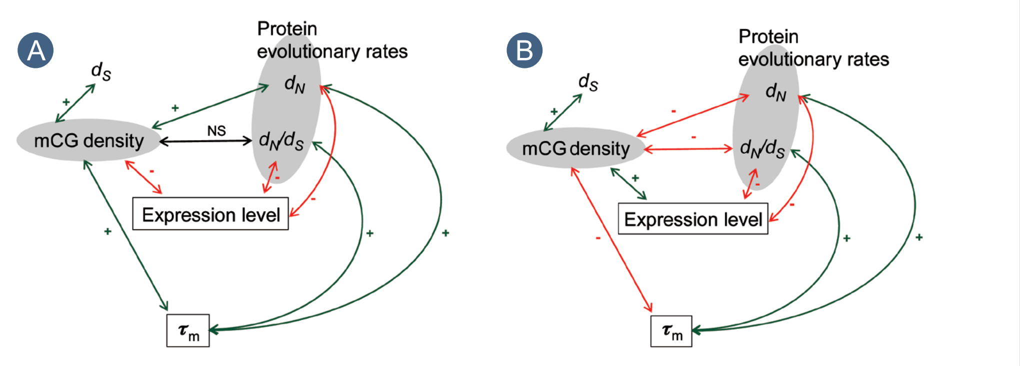
- A comparative method for identification of gene structures and alternatively spliced variants. *Bioinformatics*, 2004, *20*, 3064-79.
- ESTviewer: a web interface for visualizing mouse, rat, cattle, pig and chicken conserved ESTs in human genes and human alternatively spliced variants. *Bioinformatics*, 2005, *21*, 2510-3.
- Identification and evolutionary analysis of novel exons and alternative splicing events using cross-species EST-to-genome comparisons in human, mouse and rat. *BMC Bioinformatics*, 2006, *7*, 136.
- Plant gene and alternatively spliced variant annotator. A plant genome annotation pipeline for rice gene and alternatively spliced variant identification with cross-species expressed sequence tag conservation from seven plant species. *Plant Physiol*, 2007, *143*, 1086-95.

2. We first addressed a controversy on whether alternatively spliced exons (ASEs) evolve faster than constitutively spliced exons (CSEs). Our results indicate that ASEs evolve faster than CSEs at the protein level, but the trend is reversed at the RNA level. The effects of multiple features of ASEs on the K_A/K_S ratio test were also examined. Furthermore, different ASE patterns were shown to undergo opposite selection pressure, with CSEs in-between, suggesting that evolutionary analyses of AS should take into consideration the effects of different splicing patterns.

   We also addressed the controversy on whether duplicate genes evolve more slowly than singletons by considering gene family size conservation. Our results showed that the duplicate genes with family size conservation evolve significantly slowly than those without family size conservation, and the median evolutionary rate of singletons falls in between those of the above two types of duplicate gene families, suggesting that gene family size conservation is a good indicator of evolutionary rates.

Recently, we addressed another controversy on whether DNA methylation is correlated with increased or decreased protein evolutionary rates. Our results suggested that the first exons appear more prone to the mutagenic effects, whereas the other exons are more influenced by the regulatory effects of DNA methylation. Furthermore, we demonstrated that in mammalian exons, the correlations between DNA methylation and the conservation of individual nucleotides are dependent on the type of exonic sequence (coding or untranslated), the degeneracy of coding nucleotides, background selection pressure, and the relative position (first or non-first exon in the transcript) where the nucleotides are located. Our results suggest that the "functional resolution" of DNA methylation may be finer than previously recognized. The positive correlation between CpG methylation and the level of conservation at zero-fold degenerate nucleotides further implies that CpG methylation may serve as an "indicator" of functional importance of these nucleotides.

We also investigated the impact of two *trans*-regulatory factors, transcription factor (TF) and microRNA (miRNA), on the evolutionary rates of metazoan proteins. Our results revealed that the negative correlations between *trans*-regulation and evolutionary rates hold well across metazoans, but the strength of TF regulation as a rate indicator becomes weak when the other confounding factors that may affect evolutionary rates are controlled.

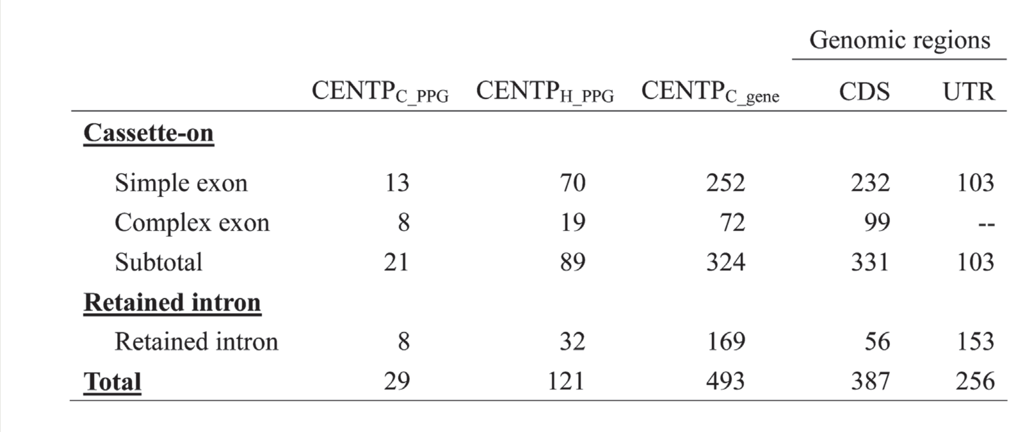


Correlations between mCG density, evolutionary rates, sample specificity of mCG Density (τm), and exon expression level in (A) first exons and (B) last/internal exons

- Alternatively and constitutively spliced exons are subject to different evolutionary forces. *Mol Biol Evol*, 2006, *23*, 675-82.
- Opposite evolutionary effects between different alternative splicing patterns. *Mol Biol Evol*, 2007, *24,* 1443-6.
- The effects of multiple features of alternatively spliced exons on the *Ka/Ks* ratio test. *BMC Bioinformatics*, 2007, *7*, 259.
- Different alternative splicing patterns are subject to opposite selection pressure for protein reading frame preservation. *BMC Evol Biol*, 2007, *7*, 179.
- Gene family size conservation is a good indicator of evolutionary rates. *Mol Biol Evol*, 2010, *27*, 1750-8.
- Position-dependent correlations between DNA methylation and the evolutionary rates of mammalian coding exons. *Proc Natl Acad Sci USA*, 2012, *109,* 15841-6.
- The impact of *trans*-regulation on the evolutionary rates of metazoan proteins. *Nucleic Acids Res*, 2013, *13*, 6371-80.
- DNA methylation is associated with an increased level of conservation at nondegenerate nucleotides in mammals. *Mol Biol Evol*, 2014, *31*, 387-96.

3. We inferred human-specific (HS) iserstions/deletions (indels) using multiple sequence alignments of mammalian genomes and thus identified >840,000 "small" indels, which affected more than 7,000 human genes (>11,000 transcripts). Functional analysis revealed that HS indels might have contributed to human unique traits by causing changes at the RNA and protein level. We further showed that HS indels may have been associated with human adaptive changes at both the species level and the subpopulation level.

   On the other hand, we developed a pipeline (CENTP) and showed that chimpanzee processed pseudogenes (PPGs), which are reverse transcribed ancient transcripts present in the current genome, can be applied to identification of novel human exons/ASVs and inference of the ancestral hominoid transcriptome and chimpanzee exon loss events. We demonstrated that the ancestral transcriptome and exon loss/gain events inferred based on comparisons of current transcripts may be incomplete (or occasionally inappropriate) because ancestral transcripts may not be represented in the ESTs of existing species. Functional analysis revealed that the novel exons identified based on chimpanzee transcripts are significantly enriched in genes related to translation regulatory activity and viral life cycle, suggesting different expression levels of the associated transcripts, and thus divergent splicing isoform composition between human and chimpanzee in these functional categories. A web interface, CNVVdb, for identification of putative copy number variations (CNVs) among 16 vertebrate species was also provided.



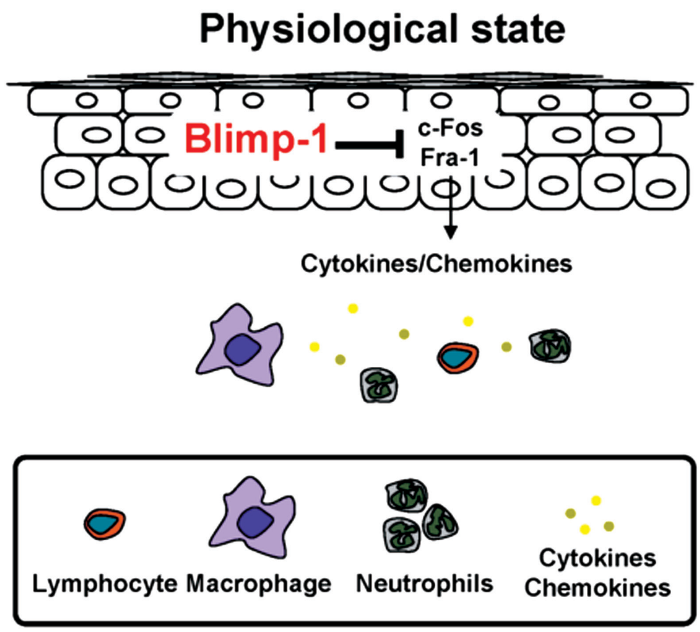
				Genomic regions	
	CENTP$_{C\_PPG}$	CENTP$_{H\_PPG}$	CENTP$_{C\_gene}$	CDS	UTR
Cassette-on					
Simple exon	13	70	252	232	103
Complex exon	8	19	72	99	--
Subtotal	21	89	324	331	103
Retained intron					
Retained intron	8	32	169	56	153
Total	29	121	493	387	256

Novel cassette-on exons and retained introns identified by CENTP

- Human-specific insertions and deletions inferred from mammalian genome sequences. *Genome Res*, 2007, *17*, 16-22.
- INDELSCAN: a web server for comparative identification of species-specific and non-species-specific insertion/deletion events, *Nucleic Acids Res*, 2007, *35*, W633-8.
- Identification and analysis of ancestral hominoid transcriptome inferred from cross-species transcript and processed pseudogene comparisons. *Genome Res*, 2008, *18*, 1163-70.
- Scanning for the signatures of positive selection for human-specific insertions and deletions. *Genome Biol Evol*, 2009, 415.
- CNVVdb: a database of copy number variations across vertebrate genomes. *Bioinformatics*, 2009, *25*, 1419-21.

4. B lymphocyte-induced maturation protein-1 (Blimp-1) is a transcriptional repressor important for the differentiation and function of several types of immune cells. Because skin serves as a physical barrier and acts as an immune sentinel, Dr. Lin's group investigated whether Blimp-1 is involved in epidermal immune function. Her group showed that Blimp-1 expression is reduced in skin lesions of some human skin

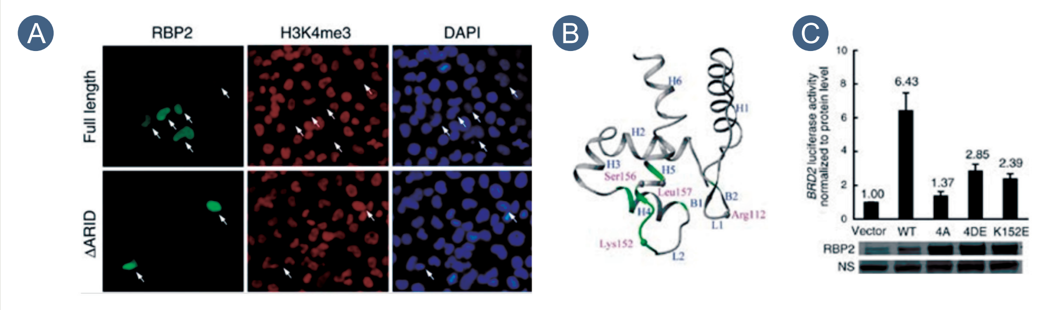
inflammatory disorders, like eczema. They thus generated a mouse line in which Blimp-1 gene, *Prdm1*, can be deleted in epidermal keratinocytes in conditional/inducible fashion to demonstrate that epidermal-specific deletion of *Prdm1* in adult mice caused spontaneously inflamed skin characterized by massive dermal infiltration of neutrophils/macrophages and development of chronic inflammation associated with higher levels of cytokines/chemokines, including G-CSF, and enhanced granulopoiesis in bone marrow. Deletion of *Prdm1* in the epidermis of adult mice also led to stronger sensitized inflammatory reactions in a disease model of contact dermatitis. The underlying mechanisms are contributed to the direct suppression of *Fos* and *Fosl1*, two positive regulators for the expression of chemokines/cytokines, by Blimp-1. Systemic increases in G-CSF are involved in the inflammatory responses because deletion of the G-CSF gene, *Csf3*, prevented neutrophilia and partially ameliorated the inflamed skin in *Prdm1*-deficient mice. Thus, they showed a new role for Blimp-1 in restraining steady-state epidermal barrier immunity.



Role for Blimp-1 in restraining steady-state epidermal barrier immunity

- Inducible deletion of the Blimp-1 gene in adult epidermis causes granulocyte-dominated chronic skin inflammation in mice. *Proc Natl Acad Sci USA*, 2013, *110*, 6476-81.

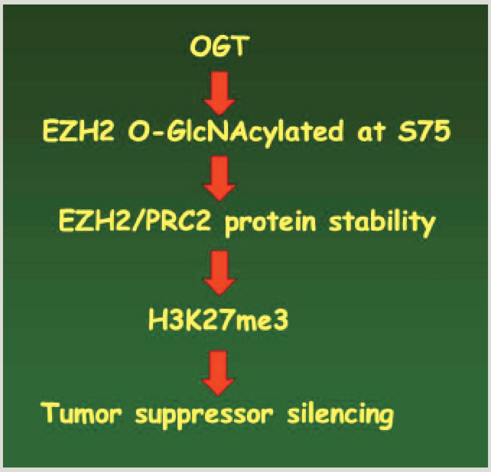
5. Histone modifiers play an essential role in epigenetics by posttranslationally modifying histone proteins to form the histone code which either disrupts the DNA/protein or protein/protein interaction or serves as a ducking site for specific transcriptional regulators to bind. One of the burning issues in the field is how histone modifiers find their target histones. Here we report that a specific sequence in DNA, namely CCGCCC, is a signal to recruit the histone demethylase RBP2. RBP2 has a unique region called ARID (abbreviation of AT-rich Interaction Domain) that can bind to DNA. Mutant RBP2 without ARID no longer removes the methyl mark from histones. ARID was demonstrated to bind CCGCCC in a pool of randomly synthesized DNA fragments and in *in vitro* binding assays. The 3-D NMR structure of the ARID was solved and 4 amino acids were pinpointed to be essential for DNA binding. Cell-based studies further indicated that DNA recognition is essential for RBP2 to regulate transcription. This work is very interesting considering that few histone modifiers recognize specific DNA sequences.



Histone demethylase RBP2 requires intact ARID domain for enzymatic and transcription regulation activities

- The ARID domain of the H3K4 demethylase RBP2 binds to a DNA CCGCCC motif. *Nat Struct Mol Biol*, 2008, *15*, 419-21.

6. O-linked N-acetylglucosamine (GlcNAc) transferase (OGT) is the only known enzyme that catalyzes the O-GlcNAcylation of proteins at the Ser or Thr side chain hydroxyl group. OGT participates in transcriptional and epigenetic regulation, and dysregulation of OGT has been implicated in diseases such as cancer. However, the underlying mechanism is largely unknown. Here we showed that OGT is required for the trimethylation of histone 3 at K27 to form the product H3K27me3, a process catalyzed by the histone methyltransferase enhancer of zeste homolog 2 (EZH2) in the polycomb repressive complex 2 (PRC2). H3K27me3 is one of the most important histone modifications to mark the transcriptionally silenced chromatin. We found that the level of H3K27me3, but not other H3 methylation products, was greatly reduced upon OGT depletion. OGT knockdown specifically down-regulated the protein stability of EZH2, without altering the levels of H3K27 demethylases UTX and JMJD3, and disrupted the integrity of the PRC2 complex. Furthermore, the interaction of OGT and EZH2/PRC2 was detected by coimmunoprecipitation and cosedimentation experiments. Importantly, we identified that serine 75 is the site for EZH2 O-GlcNAcylation, and the EZH2 mutant S75A exhibited reduction in stability. Finally, microarray and ChIP analysis have characterized a specific subset of potential tumor suppressor genes subject to repression via the OGT-EZH2 axis. Together these results indicate that OGT-mediated O-GlcNAcylation at S75 stabilizes EZH2 and hence facilitates the formation of H3K27me3. The study not only uncovers a functional posttranslational modification of EZH2 but also reveals a unique epigenetic role of OGT in regulating histone methylation.

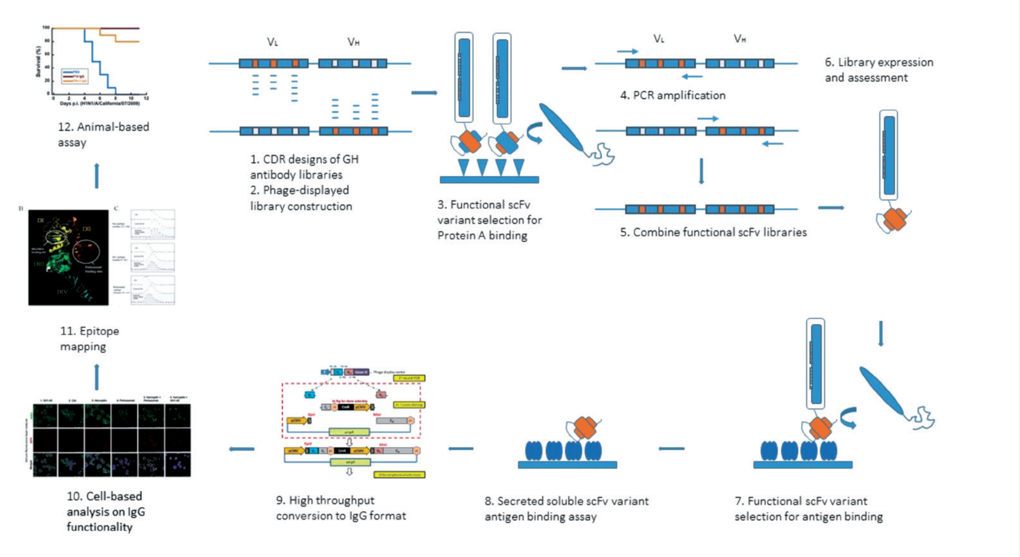


OGT-mediated EZH2 O-GlcNAcylation at S75 stabilizes EZH2/PRC2 which silence tumor suppressor gene expression through K27 trimethylation of H3

- O-GlcNAcylation regulates EZH2 protein stability and function. *Proc Natl Acad Sci USA*, 2014, *111*, 1355-60.

Development of antibody-based therapeutic for diseases

1. Our research team has accomplished in two closely interrelated disciplines (1) phage-displayed synthetic antibody library applications in antibody design, and (2) computational structural biology and structural bioinformatics for protein/antibody engineering. We design and rationalize CDR sequences for antibody-VEGF binding and to elucidate the framework sequence-stability correlations in a scFv, and to engineer broadly neutralizing antibodies against hemagglutinin in various strains of influenza virus. In parallel, we continue to establish research accomplishments in computational structural biology and structural bioinformatics: predicting sequence preferences in the CDRs for antibody-antigen interaction, and predicting protein/antibody surface residues for binding to various ligands, including protein, carbohydrate, DNA, RNA, metal ions, peptide, and small molecules. We have established computational servers http://ismblab.genomics.sinica.edu.tw/ for protein surface binding site predictions. The insights from the computational works lead to the finding that the energetically critical epitope portions are largely composed of backbone atoms, side-chain carbons, and hydrogen bond donors/acceptors. These key components are ubiquitous on protein surfaces and can be recognized by the enriched aromatic side chains and, to a lesser extent, short-chain hydrophilic residues on the antibody paratopes. Antibodies, with relatively limited sequence and structural diversities in the antigen binding sites, can recognize unlimited protein antigens through recognizing the common physicochemical features on all protein surfaces. These insights, combined with our experimental settings, have enabled the core technology – GH antibody libraries, which has begun to show its remarkable potential: we have used the GH antibody libraries to generate non-natural antibodies capable of neutralizing influenza virus for the first time.

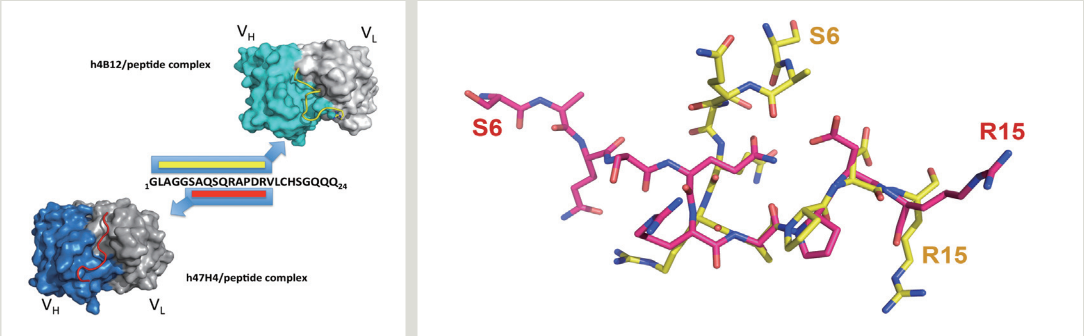


Antibody discovery with phage-displayed GH antibody libraries

- Rationalization and design of the complementarity determining region sequences in an antibody-antigen recognition interface. *PLoS ONE*, 2012, *7*, e33340.
- Protein-protein interaction site predictions with three-dimensional probability distributions of interacting atoms on protein surfaces. *PLoS ONE*, 2012, *7*, e37706.
- Prediction of carbohydrate binding sites on protein surfaces with 3-dimensional probability density distributions of interacting atoms. *PLoS ONE*, 2012, *7,* e40846.
- Loop sequence features and stability determinants in antibody variable domains by high throughput experiments. *Structure*, 2014, *22*, 9-21

- Antibody variable domain interface and framework sequence requirements for stability and function by high throughput experiments. *Structure*, 2014, *22,* 22-34.
- Origins of specificity and affinity in antibody-protein interactions. *Proc Natl Acad Sci USA*, 2014, *111*, E2656-E65.

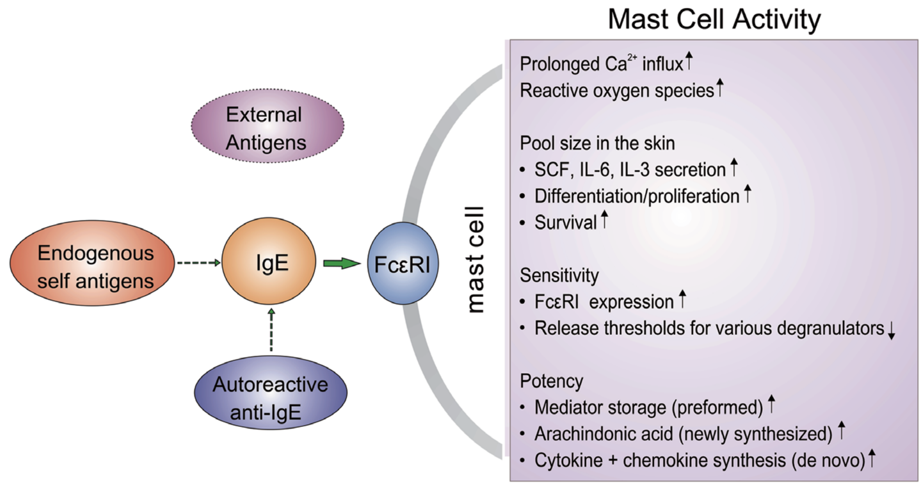
2. Dr. Tse Wen Chang previously discovered that the membrane-bound IgE on B lymphocytes in the later evolved primates species, including humans, contain a discrete domain of 52 a. a. residues, referred to as CεmX (also called M1'), located between the CH4 domain and the C-terminal transmembrane peptide of the ε heavy chain. The domain provides a very attractive site for developing immunological agents to target IgE-expressing B lymphocytes for the down-regulation of IgE in patients with various allergic diseases. A group from Genentech and our group in Academia Sinica have developed respective sets of antibodies against CεmX. One therapeutic antibody candidate 47H4 from Genentech and one therapeutic candidate 4B12 from our group recognize discrete, non-crossreactive, and yet overlapping peptide epitopes on CεmX. In collaboration with Prof. Carmay Lim's group, we have solved the X-ray crystallographic structure of 4B12 in complex with its antigenic peptide. The results showed that 4B12 and 47H4 bind to the overlapping peptide segment in drastically different conformations (Figure below). Further studies showed that the bulk of the CεmX domain exists as intrinsically disordered region. This is the first example in the literature that antibodies may be produced against an intrinsically disordered region and that two antibodies bind to a peptide in very different conformations.



The antibody 4B12 binds to GLAGGSAQSQRAPDR and the antibody 47H4 to SAQSQRAPDRVLCHS. The overlapping segment SAQSQRAPDR has very different conformations binding to the two antibodies.

- Two potential therapeutic antibodies bind to a peptide segment of membrane-bound IgE in different conformations. *Nat Commun*, 2014, *5*, 3139.

The anti-IgE therapy, omalizumab (Xolair), derived from Dr. Tse Wen Chang's invention, has been approved in more than 90 countries over the course of the past 10 years for treating patients with severe, persistent allergic asthma. Xolair was also approved in 2014 by the European Union, the USA and about 10 other countries for treating patients with chronic spontaneous urticaria (CSU), which cannot be adequately treated even with elevated doses of antihistamines. CSU, also called chronic idiopathic urticaria, is a major disease in dermatology. Since CSU is not an allergic disease and does not obviously involve IgE, how Xolair can achieve its therapeutic effect in CSU is of great interest. Dr. Chang's group in collaboration of Dr. Marcus Maurer's group at the Charite University Hospital in Berlin, Germany, provides explanations on the potential mechanisms. Dr. Maurer was the clinical investigator leading the global phase II and III trials of Xolair on CSU. They explained that the activation and degranulation of skin mast cells manifest the inflammatory process in urticaria. The binding of IgE to the high-affinity IgE receptors on mast cells raises the sensitivity of mast cells to various stimuli and augments the potency of mast cells to synthesize and release mediators (Figure below). As Xolair depletes IgE, the mast cells lose their high-affinity IgE receptors. Furthermore, the mast cells become less sensitive and raise the threshold for various degraulatory stimuli.



The binding of IgE to the high-affinity IgE receptor (FcεRI) can enhance the sensitivity of mast cells (lower the threshold) for various degranulatory stimuli

- The potential pharmacological mechanisms of omalizumab in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*, 2014, in press.

MAJOR HONORS AND AWARDS

International Academic Research Award/ 國際獎項

Year	Name	Award
2014	Wong, Chi-Huey 翁啓惠	**Wolf Prize in Chemistry, The Wolf Foundation** **沃爾夫化學獎**
	Hung, Shang-Cheng 洪上程	**David Ginsburg Memorial Lectureship from Technion-Israel Institute of Technology** **大衛 - 金斯柏格紀念講座**
		Research Grant from Japan Mizutani Foundation for Glycoscience 日本水谷糖質基金會邀請計畫
	Wu, Chung-Yi 吳宗益	**The David Y. Gin New Investigator Award, American Chemical Society** **美國化學會醣科學學門年輕研究學者獎**
2013	Chen, Chien-Jen 陳建仁	Knight, Pontifical Equestrian Order of St. Gregory the Great, Vatican 梵諦岡宗座聖大額我略爵士
	Hung, Shang-Cheng 洪上程	Asian Core Program (ACP) Lectureship Award 亞洲核心尖端有機聯盟訪馬來西亞系列演講獎
2012	Wong, Chi-Huey 翁啓惠	**Arthur C. Cope Award, American Chemical Society, USA** **美國化學協會亞瑟科博獎**
		Nikkei Asia Prize for Science, Technology and Innovation, Japan **日經亞洲獎**
		Distinguished Fellow, University of Malaya 馬來西亞大學榮譽特聘研究員
	Chen, Chien-Jen 陳建仁	**Knowledge for the World Award, Johns Hopkins University** **美國霍普金斯大學 Knowledge for the World 獎**
	Lee, Wen-Hwa 李文華	**Elected Fellow, American Association for the Advancement of Science (AAAS), USA** **美國科學促進會會士**
	Chuang, Trees-Juen 莊樹諄	**The Pontifical Academy of Sciences, Vatican** **庇護十一世勳章**
	Juan, Li-Jung 阮麗蓉	Best 5 Articles in Cell Reports, 2012 2012 年度 Cell Reports Best 5 文章
	Shen, Chia-Ning 沈家寧	Travel award of International Society of Stem Cell Research, 2012 國際幹細胞學會 2012 年度 Travel Award
2011	Chen, Chien-Jen 陳建仁	14th Prof. Vikit Viranuvatti Lecture, Gastroenterology Association of Thailand 泰國消化系學會 Prof. Vikit Viranuvatti 紀念講座
	Hung, Shang-Cheng 洪上程	Asian Core Program (ACP) Lectureship Award 亞洲核心尖端有機聯盟訪新加坡系列演講獎
		Member, Editorial Board, Carbohydrate Research Carbohydrate Research 期刊編輯委員
2010	Wong, Chi-Huey 翁啓惠	**Fellowship, American Academy of Arts and Sciences, USA** **美國人文與科學院院士**
		Elected Associate Member, European Molecular Biology Organization (EMBO) 歐洲分子生物組織外籍會士
	Chen, Chien-Jen 陳建仁	**Member, Delta Omega Alpha Society, Johns Hopkins University, USA** **美國約翰霍普金斯大學 Delta Omega 榮譽會會員**
		Knight, Equestrian Order of the Holy Sepulchre of Jerusalem, Vatican
	Li, Wen-Hsiung 李文雄	Fellowship, American Academy of Arts and Sciences, USA 美國人文與科學院院士
	Juan, Li-Jung 阮麗蓉	Asia-Pacific International Molecular Biology Network (A-IMBN) Feature Report, 2010 亞太國際分子生物學網絡 2010 年專題報導

Year	Name	Award
2009	Wong, Chi-Huey 翁啓惠	Honorary Doctorate, City University of Hong Kong, Hong Kong 香港城市大學榮譽理學博士
	Chen, Chien-Jen 陳建仁	**Science and Engineering Award, Taiwanese-American Foundation Award, USA** **台美文教基金會台灣傑出人才成就獎 - 科技工程獎**
		Officier dans l’Ordre des Palmes Academiques, Ministry of Education, France **法國教育部二等學術勳章**
	Chen, Chung-Hsuan 陳仲瑄	**Fellow, American Association for the Advancement of Science (AAAS), USA** **美國科學促進學會會士**
	Li, Wen-Hsiung 李文雄	**Mendel Medal, the Genetics Society of UK** **英國遺傳學會孟德爾獎章**
		Fellow, The Academy of Sciences for the Developing World (TWAS) **發展中世界科學院院士**
	Yu, Alice Ling-Tsing 陳鈴津	St. Baldrick's COG Neuroblastoma Laboratory Award, USA 美國 St. Baldrick's 基金會兒童腫瘤 - 神經母細胞瘤研究獎
	Ma, Che Alex 馬 徹	**Young Affiliate, The Academy of Sciences for the Developing World (TWAS)** **發展中世界科學院年輕學者**
2008	Wong, Chi-Huey 翁啓惠	**The F.A. Cotton Medal for Excellence in Chemical Research, USA** **美國化學研究卡頓獎章**
	Chen, Chien-Jen 陳建仁	**Dr. DV Datta Memorial Oration, Indian National Association for Study of the Liver, India** **印度國家肝臟研究學會 Dr. D. V. Datta 紀念講座**
		Cutter Lecture on Preventive Medicine, Harvard University, USA **美國哈佛大學 Cutter 講座**
	Li, Wen-Hsiung 李文雄	**Chen Award for Distinguished Academic Achievement in Human Genetic and Genomic Research, Human Genome Organization, USA** **人類遺傳與基因體研究傑出學術成就獎**
	Tsai, Ming-Daw 蔡明道	Distinguished Alumnus Award, Purdue University School of Pharmacy 美國普渡大學藥學院傑出校友獎
	Lin, Kuo-I 林國儀	**1st ASAIHL-Scopus Young Scientist Award** **第一屆東亞青年科學家生命科學獎**
	Juan, Li-Jung 阮麗蓉	Asia-Pacific International Molecular Biology Network (A-IMBN) Feature Report, 2008 亞太國際分子生物學網絡 2008 年專題報導
2007	Wong, Chi-Huey 翁啓惠	**Elected Fellow, The Academy of Sciences for the Developing World (TWAS)** **發展中世界科學院院士**
		Honorary Doctorate, Scientiarum Honoris Causa, Technion – Israel Institute of Technology, Israel 以色列科技研究院最高榮譽博士
		Honorary Fellow, the Chemical Research Society of India (CRSI), India 印度化學研究協會榮譽院士
		Science and Engineering Achievement Award, Taiwanese American Foundation (TAF) 台美基金會傑出人才成就獎科技工程獎項
	Chen, Chien-Jen 陳建仁	Honorary Member, Mongolian Academy of Sciences, Mongolia 蒙古科學院名譽院士
	Chang, Tse-Wen 張子文	**Distinguished Achievement Award, Chinese Institute of Engineers, USA** **美洲中國工程師學會傑出成就獎**
		Honorary Fellow Award, American Academy of Allergy, Asthma, and Immunology (AAAAI), USA **美國過敏、哮喘與免疫學協會醫學獎**
	Li, Wen-Hsiung 李文雄	Cockerham Lecture, North Carolina State University, USA 美國北卡州立大學 Cockerham 講座
2006	Wong, Chi-Huey 翁啓惠	**Humboldt Research Award for Senior Scientists, Germany** **德國宏博資深科學家獎**
		The Georges Smets Chair Award for Organic or Polymer Chemistry, Louvain-la-Neuve, Belgium
	Chang, Tse-Wen 張子文	Xolair Chosen for Prix Galien Award for Outstanding Innovation in R&D, UK
		Nature Biotechnology’s Shortlist of Personalities Who Made the Most Significant Contribution to Biotech in the Past 10 Years

Year	Name	Award
2006	Hung, Shang-Cheng 洪上程	Asian Core Program (ACP) Lectureship Award 亞洲核心尖端有機聯盟訪日、韓系列演講獎
2005	Wong, Chi-Huey 翁啓惠	**Award for Creative Work in Synthetic Organic Chemistry, American Chemical Society, USA 美國化學會合成有機化學創意傑作獎**
		Elected Fellow, the American Association for the Advancement of Science (AAAS) 美國科學促進學會會士
	Li, Wen-Hsiung 李文雄	**Science and Engineering Achievement Award, Taiwanese American Foundation (TAF) 台美文教基金會台灣傑出人才成就獎 - 科技工程獎**
		James D. Watson Professor, Chicago University 美國芝加哥大學 James D. Watson 教授
	Lin, Kuo-I 林國儀	**Li Foundation Heritage Prize, USA 美國李氏傳統基金會獎**
2004	Li, Wen-Hsiung 李文雄	**Horace Mann Medal, Brown University 美國布朗大學 Horace Mann 獎章**
2003	Li, Wen-Hsiung 李文雄	**Balzan Prize in Genetics and Evolution, Italy 國際巴仁科學暨藝術獎：遺傳與演化組**
		Member, The US National Academy of Sciences, USA 美國國家科學院院士
		George Beadle Professor, Chicago University 美國芝加哥大學 George Beadle 教授
	Tsai, Ming-Daw 蔡明道	Kimberly Professor of Chemistry, Ohio State University 美國俄亥俄州立大學特約講座教授
		Guest Professor of Tsinghua University, PRC 中國清華大學化學系客座教授
		President of Chinese American Chemical Society 美洲華人化學學會主席

Domestic Academic Research Award/ 國內獎項

Year	Name	Award
2014	Lin, Kuo-I 林國儀	**Young Scientist Research Award, TienTe Lee Biomedical Foundation 第九屆李天德青年科學家學術研究獎**
	Chen, Yun-Ru Ruby 陳韻如	**Promising Women in Science Award, Wu Chieh Shiung Education Foundation 第七屆台灣傑出女科學家新秀獎**
	Li, Tsung-Lin 李宗璘	Career Development Award, Academia Sinica, Taiwan 中央研究院前瞻計畫獎
	Ma, Che Alex 馬 徹	**TBF Chairs in Biotechnology, The Taiwan Bio-Development Foundation 台灣生技醫藥發展基金會 TBF 生技講座**
		Exceptional Merit in Academic Award from Chung Hwa Rotary Educational Foundation 中華扶輪社卓越學術貢獻獎
	Wu, Chung-Yi 吳宗益	**TBF Chairs in Biotechnology, The Taiwan Bio-Development Foundation 台灣生技醫藥發展基金會 TBF 生技講座**
		Outstanding Alumni, Department of Applied Chemistry, National Chiao-Tung University 交通大學傑出校友
2013	Chen, Chien-Jen 陳建仁	**Outstanding Contribution in Science and Technology Award, Executive Yuan 行政院傑出科技貢獻獎**
	Chang, Tse-Wen 張子文	Lifetime Achievement Award in Allergy, Taiwan Academy of Pediatric Allergy Asthma and Clinical Immunology 台灣兒童過敏氣喘免疫及風濕病醫學會終身成就獎
	Heish, Shie-Liang 謝世良	**Outstanding Research Award, TienTe Lee Biomedical Foundation 第八屆永信李天德卓越醫藥科技獎**
	Hung, Shang-Cheng 洪上程	**Outstanding Research Award, Ho Chin Tui Foundation 侯金堆數理科學組傑出榮譽獎**

Year	Name	Award
2013	Lin, Kuo-I 林國儀	**Outstanding Research Award, National Science Council** **行政院國科會傑出研究獎**
	Chen, Yun-Ru Ruby 陳韻如	**Young Investigator Award, Biophysical Society of ROC** **中華民國生物物理學會傑出年輕學者獎**
	Ma, Che Alex 馬 徹	Career Development Award, Academia Sinica 中央研究院前瞻計畫獎
	Yang, Hwai-I 楊懷壹	**Da-You Wu Memorial Award, National Science Council** **行政院國科會吳大猷先生紀念獎**
		Outstanding Contribution in Science and Technology Award, Executive Yuan **行政院傑出科技貢獻獎**
2012	Chen, Chien-Jen 陳建仁	**Science Profession Medal (First Class), National Science Council** **行政院國科會科學專業獎一等獎章**
	Hung, Shang-Cheng 洪上程	**Academic Awards of Ministry of Education** **教育部第五十六屆學術獎 - 數學及自然科學類科**
		Outstanding Research Award, TienTe Lee Biomedical Foundation **第七屆李天德卓越醫藥科技獎**
		Outstanding Research Award, National Science Council **行政院國科會傑出研究獎**
	Ma, Che Alex 馬 徹	Academia Sinica Significant Research, 2012 中央研究院 2012 年度 - 重要發現與突破
	Wang, Yi-Sheng 王亦生	Career Development Award, Academia Sinica 中央研究院前瞻計畫獎
	Wu, Chung-Yi 吳宗益	**Academia Sinica Research Award for Junior Research Investigators** **中央研究院年輕學者研究著作獎**
		Career Development Award, Academia Sinica 中央研究院前瞻計畫獎
2011	Wong, Chi-Huey 翁啓惠	Honorary Doctorate, National Chiao Tung University 國立交通大學榮譽理學博士
		Honorary Doctorate, National Tsing Hua University 國立清華大學榮譽理學博士
		Honorary Doctorate, Kaohsiung Medical University 高雄醫學大學榮譽理學博士
	Chen, Chien-Jen 陳建仁	Excellence in Cancer Prevention Award, Taiwan Joint Cancer Conference 台灣癌症聯合學術年會台灣癌症防治貢獻獎
	Yu, Alice Ling-Tsing 陳鈴津	**Academic Awards of Ministry of Education** **教育部第五十五屆學術獎 - 生物及醫農科學類科**
	Ma, Che Alex 馬 徹	**Young Scientist Award, TienTe Lee Biomedical Foundation** **第六屆李天德青年科學家學術研究獎**
	Wang, Yi-Sheng 王亦生	Young Researcher Award, Taiwan Society for Mass Spectrometry 台灣質譜學會青年學者研究獎
2010	Wong, Chi-Huey 翁啓惠	Honorary Doctorate, National Chung Hsing University 國立中興大學榮譽理學博士
	Chen, Chien-Jen 陳建仁	Outstanding Merit Award, Wang Ming-Ning Memorial Foundation 第二十屆王民寧獎
		Investigator Award, Academia Sinica 中央研究院深耕計畫獎
	Chen, Chung-Hsuan 陳仲瑄	**Member, Academia Sinica** **第二十八屆中央研究院院士**
	Hung, Shang-Cheng 洪上程	**The Advancement of Outstanding Scholarship Award, Foundation for the Advancement of Outstanding Scholarship** **傑出人才發展基金會傑出人才講座**
		Teco Award, Teco Technology Foundation 第十七屆東元科技獎 - 化工生物醫工領域
		Investigator Award, Academia Sinica 中央研究院深耕計畫獎
	Lin, Kuo-I 林國儀	Career Development Award, Academia Sinica 中央研究院前瞻計畫獎
	Ma, Che Alex 馬 徹	**Academia Sinica Research Awards for Junior Research Investigators** **中央研究院年輕學者研究著作獎**
		Two research highlights in Taiwan Yearbook of Science and Technology, 2010 台灣科技年鑑 2010 年度 - 重要研究

Year	Name	Award
2009	Yu, Alice Ling-Tsing 陳鈴津	Wang Ming-Ning Award 第十九屆王民寧獎
	Hung, Shang-Cheng 洪上程	**Outstanding Research Award, National Science Council** **行政院國科會傑出研究獎**
		Academic Publication Award, Chung-Shan Academic & Cultural Foundation 中山學術文化基金會中山學術著作獎
		Best Article Award in Taipei Chemical Society, 2009 中國化學會年度最佳論文獎
		Investigator Award, Academia Sinica, Taiwan 中央研究院深耕計畫獎
	Juan, Li-Jung 阮麗蓉	Yang Scientist Research Award, TienTe Lee Biomedical Foundation 第四屆李天德青年科學家學術研究獎
		Career Development Award, Academia Sinica 中央研究院前瞻計畫獎
2008	Wong, Chi-Huey 翁啓惠	**National Science Council (NSC) Science Professional Medal** **行政院國科會科學專業獎一等獎章**
		Honorary Doctorate, National Sun Yat-sen University 國立中山大學名譽理學博士
	Hung, Shang-Cheng 洪上程	Distinguished Teaching Award, National Tsing Hua University 國立清華大學傑出教學獎
		Yu-Ziang Hsu Scientific Paper Award, Far Eastern Y. Z. Hsu Science and Technology Memorial Foundation 第六屆有庠科技論文獎
	Juan, Li-Jung 阮麗蓉	Academia Sinica Major Discovery, 2008 中央研究院 2008 年度 - 重要發現與突破
2007	Wong, Chi-Huey 翁啓惠	Honorary Doctorate, National Yang-Ming University 國立陽明大學榮譽理學博士
	Hung, Shang-Cheng 洪上程	行政院國科會台灣學術里程與科技前瞻計畫
		Distinguished Professor, National Tsing Hua University 國立清華大學特聘教授
	Chuang, Trees-Juen 莊樹諄	**Academia Sinica Research Awards for Junior Research Investigators** **中央研究院年輕學者研究著作獎**
		Wu Da-You Memorial Award, National Science Council **行政院國科會吳大猷先生紀念獎**
2006	Chen, Chung-Hsuan 陳仲瑄	Investigator Award, Academia Sinica 中央研究院深耕計畫獎
2005	Li, Wen-Hsiung 李文雄	Distinguished Chair Professor, Dept. of Computer Science and Information Engineering, Nation Taiwan University 台灣大學資訊工程系特聘研究講座
	Hung, Shang-Cheng 洪上程	Outstanding Youth Medal, China Youth Corps 中國青年救國團青年獎章
2004	Chen, Chung-Hsuan 陳仲瑄	**The Advancement of Outstanding Scholarship Award, Foundation for the Advancement of Outstanding Scholarship** **傑出人才發展基金會傑出人才獎座**
2003	Wong, Chi-Huey 翁啓惠	Distinguished Professor of Chemistry and Biochemical Sciences, National Taiwan University 台大化學與生化科學特聘講座教授

ORGANIZATION

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林世昌 Su-Chang Lin
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侯武勳 Wu-Shiun Hou
李文華 Wen-Hwa Lee
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呂仁 Jean Lu

Physical and Computational Genomics Division

Division Director: 陳仲瑄 Chung-Hsuan Chen

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Biotechnology Incubation Center

Division Director: 梁啓銘 Chi-Ming Liang

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蔡淑芳 Daisy Tsai

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林素琴 Annie S. C. Lin
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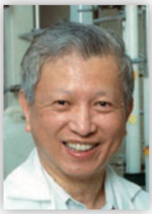
李淑卿 Annie Lee

SCIENTIFIC ADVISORY BOARD

This board helps to provides advice to the Center on its research programs and future direction and evaluate all appointments of senior personnel proposed by the Center.



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DIVISIONS AND RESEARCH SCIENTISTS

- Chemical Biology Division
- Medical Biology Division
- Physical and Computational Genomics Division
- Biotechnology Incubation Center
- Research Specialists

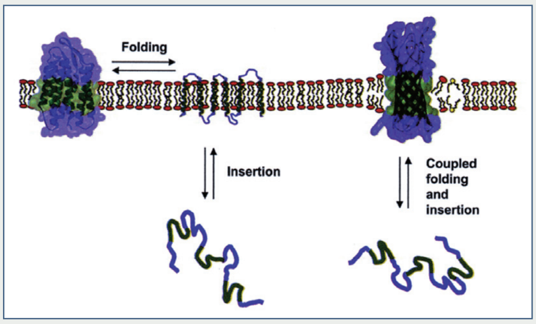
Chemical Biology Division

The main thrust of this division is to develop chemical and biological approaches to understand and solve problems in living systems. Current research programs include mechanism-based and structure-based drug discoveries, development of high-throughput systems to facilitate the process, design of new molecular probes for imaging and glycoproteomic analysis, development of glycan arrays for the high-throughput analysis of biomolecular interactions, and development of new reactions and methods of interest to functional genomic study and drug discoveries. In addition, efforts are directed toward identification and validation of important targets associated with cancer and infection, and protein misfolding diseases, and understanding of the function of these targets at the molecular level. Using the state-of-the-art mass spectrometry, NMR, and X-ray crystallography as well as other genomic and proteomic approaches, the division is developing new strategies to tackle the problems of protein folding, structure and function, especially that of membrane glycoproteins and intracellular proteins associated with cancer, infectious diseases and the immune system.

The following subjects are of current interest.

- **Membrane protein: structure-function study and drug design.** Transglycosylase, hemagglutinin, neuraminidase and other glycoprotein markers on bacteria, viruses, cancer cells and immune cells.
- **Carbohydrate chemistry and biology.** New synthetic chemistry, glycan sequencing, glycan arrays for analysis of sugar-protein interaction, sugar-based drug discovery and vaccine design.
- **High-throughput screening and drug discovery**. Development of diverse structure space and assays for target-based and cell-based screen, e.g., transglycosylase of drug resistant bacteria, HCV, influenza, cancer, and directed evolution of enzymes for biofuel synthesis.
- **Modification of biomolecules and protein design.** Protein design by computation and phage-display: high-order structures, human antibody library. Synthetic biology and natural product chemistry: synthesis of new antibiotics, biofuels and other bioactive molecules. Protein misfolding and disease progression.
- **Post-translational glycosylation and epigenetic regulation:** Glycoprotein synthesis, human antibody, and vaccine design. Probing the effect of glycosylation on protein structure and function. Chromatin methylation and demethylation associated with cancer and viral diseases.

This division will continue its long-term plan in the discovery and development of new chemistry and technology to solve emerging scientific, medical, and biotech problems. The middle-term efforts are devoted to the following areas: (1) solving technology hurdles in glycomics research, i.e. glycan synthesis, sequencing, and analysis, (2) tackling the problems of infectious diseases, in particular, influenza, HCV, and drug resistant bacteria, such as MRSA and TB, (3) development of new probes for biomarker discovery in cancer and cancer stem cells and novel vaccine development, (4) identification of novel therapeutic components from natural products, (5) drug discovery using the ultra-HTS system, and (6) functional proteomics – study of structure, folding, function (in vitro and in vivo), mechanisms, modifications (methylation, phosphorylation and glycosylation), interactions, and therapeutic application. In addition to pursuing new chemistry and technology discovery, the division is intended to translate important discoveries into disease diagnosis, vaccines, and drug developments.



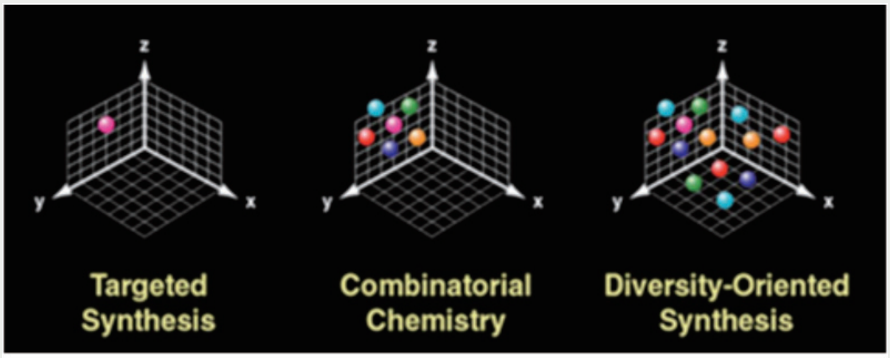
化學生物學專題中心

本專題中心的主要的研究重點在利用化學與生物學的方法來瞭解及解決生命系統的問題，目前的研究興趣包括進行以反應機制與結構為基礎的藥物研發、發展超高速篩選系統、尋找適用於影像分析與醣蛋白質體研究的新分子探針、製備醣晶片以高速檢測生物分子作用，尋找新的化學方法進行功能基因體學研究及藥物開發。主要重點在瞭解如癌症與傳染疾病之主要標的物的功能及致病原因，蛋白質錯誤摺疊所衍生的疾病，開發新的方法與策略來研究這些標的物在分子層次的作用機制。利用新穎的質譜儀、核磁共振和 X 光結晶學以及其他基因體與蛋白質體的方法，來處理蛋白質摺疊問題及標的蛋白的結構與功能問題，近期著重在細胞膜蛋白、醣蛋白及細胞內蛋白的訊號傳送。

目前的主要研究項目有：

- **膜蛋白上結構及功能為基礎的藥物設計**：尋找及研究在細菌、病毒和癌症細胞上的標誌，紅血球凝聚素，唾液酸苷酶和其他醣蛋白標誌物。
- **醣化學與醣生物學研究**：研究新的合成化學，醣分子定序，及用「醣晶片」分析醣與蛋白質間交互作用及發展以「醣」為基礎的藥物研究和疫苗設計。
- **高速篩選系統和藥物研發**：利用分生及生化技術發展不同空間架構和分析方法，結合「藥物標的」及「細胞內活性」之偵測系統進行高速藥物篩選，選擇具活性之化合物；例如篩選可抗多重耐藥性細菌轉醣酶之抑制劑，C肝炎病毒，流感，癌症和以演化的方法改良製造生質能的酵素。
- **生物分子的修飾和蛋白質設計**：利用計算生物學與生物資訊技術設計穩定的蛋白質分子，再藉由噬菌體表達，篩選具有高度穩定性與專一性功能的蛋白質分子。合成生物學和天然物化學：合成新抗菌素，生質能源和其他具生物活性分子。瞭解蛋白質錯誤摺疊與疾病的關係。
- **後轉譯醣化與表觀遺傳調控**：醣蛋白合成，人類抗體，疫苗設計。探測「醣化」對蛋白質結構和功能的影響。染色質甲基化與去甲基化與癌症和病毒性疾病相關研究，與針對癌症和病毒性疾病的染色質與組蛋白後修飾對於調控及表觀（phenotype）的影響。

本專題中心將持續我們的長期目標以「新的」化學和技術解決新興的科學，醫學，和生物問題。我們的中程目標將致力於 (1) 解決「醣化學」研究過程中的技術障礙，包括醣的合成、定序及分析，(2) 傳染病的問題：解決流感、C 肝炎病毒和抗藥細菌的問題，例如超級金黃色葡萄球菌和肺結核，(3) 確認開發癌症和癌幹細胞的標誌物質及疫苗，(4) 自天然物中尋找獨特治病成分，(5) 使用超高速藥物篩選系統尋找先導藥物及進行其他應用，(6) 蛋白質和蛋白質體學 - 研究蛋白質的架構、摺疊、功能 (體外、體內)、作用、修飾 (甲基化、磺酸基化和醣基化)、交互作用，作為藥物標的和發展治療劑。此外，在追求新化學和技術過程中，我們會將新的發現和技術應用在可能的疾病診斷，疫苗和藥物開發。



Chi-Huey Wong 翁啓惠

President, Academia Sinica
Distinguished Research Fellow and Division Director of Chemical Biology, Genomics Research Center
中央研究院院長
基因體研究中心特聘研究員兼化學生物專題中心執行長
chwong@gate.sinica.edu.tw

Education and Positions

- Ph.D., Chemistry, Massachusetts Institute of Technology, 1982
- Postdoctoral Fellow, Harvard University, 1982-1983
- Assistant Professor through Professor of Chemistry and Biochemistry, Texas A&M University, 1983-1989
- Professor and Ernest W. Hahn Chair in Chemistry, The Scripps Research Institute, 1989-2006
- Head, Frontier Research Program on Glycotechnology, Institute of Physical and Chemical Research (RIKEN), Japan, 1991-1999
- Member, The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 1996-2006
- Director, The Genomics Research Center, Academia Sinica, Taipei, Taiwan, 2003-2006
- President, Academia Sinica, Taipei, Taiwan, 2006-present
- Joint Appointment: Professor of Chemistry, The Scripps Research Institute; Distinguished Professor of Chemistry and Biochemical Sciences, National Taiwan University

Honors

- Searle Scholar Award in Biomedical Sciences, 1985
- Presidential Young Investigator in Chemistry, 1986
- Editor-in-Chief, Bioorganic & Medicinal Chemistry, 1993-2010
- The IUPAC International Carbohydrate Award, 1994
- Elected Member of Academia Sinica, Taipei, 1994
- Elected Member of the American Academy of Arts and Sciences, 1996
- American Chemical Society Harrison Howe Award in Chemistry, 1998
- American Chemical Society Claude S. Hudson Award in Carbohydrate Chemistry, 1999
- The International Enzyme Engineering Award, 1999
- Presidential Green Chemistry Award, USA, 2000
- Elected Member of the National Academy of Sciences, USA, 2002
- American Chemical Society Award for Creative Work in Synthetic Organic Chemistry, 2005
- The F. A. Cotton Medal for Excellence in Chemical Research, 2008
- Elected Associate Member of the European Molecular Biology Organization (EMBO), 2010
- The American Chemical Society Arthur C. Cope Award, 2012
- Nikkei Asia Prize for Science, Technology and Innovation, 2012
- Wolf Prize in Chemistry, 2014

Selected Publications

- Heine, A.; DeSantis, G.; Luz, J. G.; Mitchell, M.; Wong, C. H.; Wilson, I. A., Observation of covalent intermediates in an enzyme mechanism at atomic resolution. *Science*, 2001, *294*, 369-74.

- Sears, P.; Wong, C. H., Toward automated synthesis of oligosaccharides and glycoproteins. *Science*, 2001, *291,* 2344-50.

- Hsu, T. L.; Hanson, S. R.; Kishikawa, K.; Wang, S. K.; Sawa, M.; Wong, C. H., Alkynyl sugar analogs for the labeling and visualization of glycoconjugates in cells. *Proc Natl Acad Sci USA*, 2007, *104*, 2614-9.

- Hanson, S. R.; Culyba, E. K.; Hsu, T. L.; Wong, C. H.; Kelly, J. W.; Powers, E. T., The core trisaccharide of an N-linked glycoprotein intrinsically accelerates folding and enhances stability. *Proc Natl Acad Sci USA*, 2009, *106*, 3131-6.
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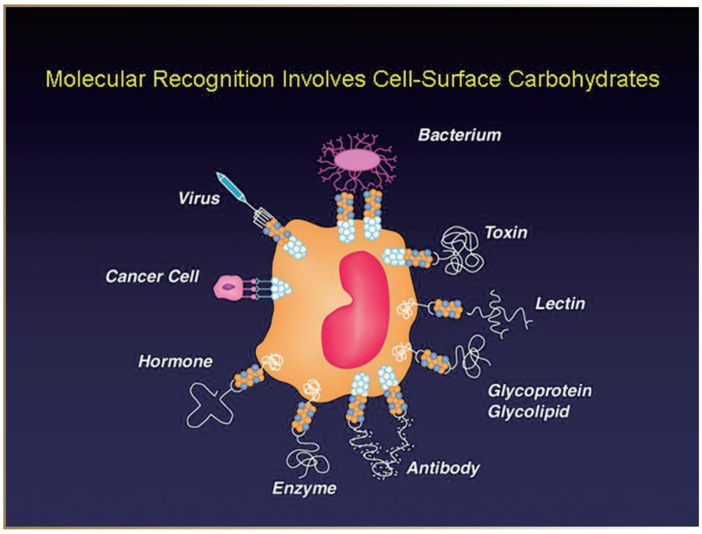
- Liu, Y. C.; Yen, H. Y.; Chen, C. Y.; Chen, C. H.; Cheng, P. F.; Juan, Y. H.; Khoo, K. H.; Yu, C. J.; Yang, P. C.; Hsu, T. L.; Wong, C. H., Sialylation and fucosylation of epidermal growth factor receptor suppress its dimerization and activation in lung cancer cells. *Proc Natl Acad Sci USA*, 2011, *108*, 11332-7.
- Hsu, C. H.; Hung, S. C.; Wu, C. Y.; Wong, C. H., Toward automated oligosaccharide synthesis. *Angew Chem Int Ed*, 2011, *50*, 11872-923.
- Chu, K. C.; Ren, C. T.; Lu, C. P.; Hsu, C. H.; Sun, T. H.; Han, J. L.; Pal, B.; Chao, T. A.; Lin, Y. F.; Wu, S. H.; Wong, C. H.; Wu, C. Y., Efficient and stereoselective synthesis of α(2→9) oligosialic acids: from monomers to dodecamers. *Angew Chem Int Ed*, 2011, *50*, 9391-5.
- Huang, C. Y.; Shih, H. W.; Lin, L. Y.; Tien, Y. W.; Cheng, T. J. R.; Cheng, W. C.; Wong, C. H.; Ma, C., Crystal structure of *Staphylococcus aureus* transglycosylase in complex with a lipid II analog and elucidation of peptidoglycan synthesis mechanism. *Proc Natl Acad Sci USA*, 2012, *109*, 6496-501.
- Huang, Y. L.; Hung, J. T.; Cheung, S. K.; Lee, H. Y.; Chu, K. C.; Li, S. T.; Lin, Y. C.; Ren, C. T.; Cheng, T. J. R.; Hsu, T. L.; Yu, A. L.; Wu, C. Y.; Wong, C. H., Carbohydrate-based vaccines with a glycolipid adjuvant for breast cancer. *Proc Natl Acad Sci USA*, 2013, *110*, 2517-22.

Research Interests

Chemical Biology and Drug Discovery

Research in the Wong lab encompasses a broad spectrum of bioorganic and synthetic chemistry. Development of small molecules targeting proteins and RNA has been performed to investigate how small molecules interact with biologically important molecules and in turn, learn more about the function of those molecules. Development of both synthetic and bioorganic strategies is also paramount to our research. Programmable one-pot reactions are being developed for the synthesis of complex oligosaccharides and glycan arrays and compliment new strategies for the assembly of vaccines, glycoproteins and other biologically active molecules to tackle major problems in biology, especially those associated with cancer, infectious diseases and immune system.

我們的研究工作主要著重於化學生物及新藥研發。從瞭解致病基因的功能及機制去設計並合成小分子來進一步研究其與標的物的作用，進而研發出新的檢測方法及新藥。目前重點放在瞭解醣分子在細胞表面所扮演的角色，醣蛋白合成方法的發展，醣晶片的設計與應用，及酵素抑制劑的設計與合成。希望將來能發展新的藥物以供抗癌、抗病毒與抗細菌的研究。


Molecular Recognition Involves Cell-Surface Carbohydrates

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Education and Positions

- Ph.D., Chemistry, National Tsing Hua University, 1992
- Postdoctoral Fellow, University of California at Berkeley, USA, 1994-1995
- Postdoctoral Fellow, The Scripps Research Institute, USA, 1995-1998
- Assistant Research Fellow, Institute of Chemistry, Academia Sinica, 1998-2002
- Associate Research Fellow, Institute of Chemistry, Academia Sinica, 2002-2005
- Associate Professor, Department of Chemistry, National Tsing Hua University, 2005-2006
- Professor, Department of Chemistry, National Tsing Hua University, 2006-2009
- Research Fellow, Genomics Research Center, Academia Sinica, 2009-2012
- Distinguished Research Fellow, Genomics Research Center, Academia Sinica, 2012-present

Honors

- Wu Ta-You Memorial Award, National Science Council, Taiwan, 2003
- Outstanding Research Award, National Science Council, 2004/2009/2012 (3 times)
- Yu-Ziang Hsu Scientific Paper Award, Far Eastern Y. Z. Hsu Science and Technology Memorial Foundation, 2008
- Distinguished Teaching Award, National Tsing Hua University, 2008
- Investigator Award, Academia Sinica, 2009
- Academic Publication Award, Chung-Shan Academic & Cultural Foundation, 2009
- 17th Teco Award, Teco Technology Foundation, 2010
- Outstanding Scholar Chair, Foundation for the Advancement of Outstanding Scholarship (FAOS), 2010
- 7th Outstanding Biomedical Technology Award, TienTe Lee Biomedical Foundation, 2011
- 56th Academic Award, Ministry of Education, 2012
- Ho Chin Tui Outstanding Research Award, Ho Chin Tui Foundation, 2013
- David Ginsburg Memorial Lectureship Award, Israel, 2014

Selected Publications

- Hung, S.-C.; Thopate, S. R.; Chi, F.-C.; Chang, S.-W.; Lee, J.-C.; Wang, C.-C.; Wen, Y.-S., 1,6-Anhydro-β-L-hexopyranoses as potent synthons in the synthesis of the disaccharide units of bleomycin A_2 and heparin. J Am Chem Soc, 2001, 123, 3153-4.
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- Hu, Y.-P.; Lin, S.-Y.; Huang, C.-Y.; Zulueta, M. M. L.; Liu, J.-Y.; Chang, W.; Hung, S.-C., Synthesis of 3-O-sulfonated cell-surface heparan sulfate octasaccharides that inhibit herpes simplex virus type 1 host-cell interaction. Nat Chem, 2011, 3, 557-63.
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- Hsu, Y.; Ma, H.-H.; Lico, L. S.; Jan, J.-T.; Fukase, K.; Uchinashi, Y.; Zulueta, M. M. L.; Hung, S.-C., One-pot synthesis of N-acetyl- and N-glycolylneuraminic acid capped trisaccharides and evaluation of their influenza A(H1 N1) inhibition. Angew Chem Int Ed, 2014, 53, 2413-6.

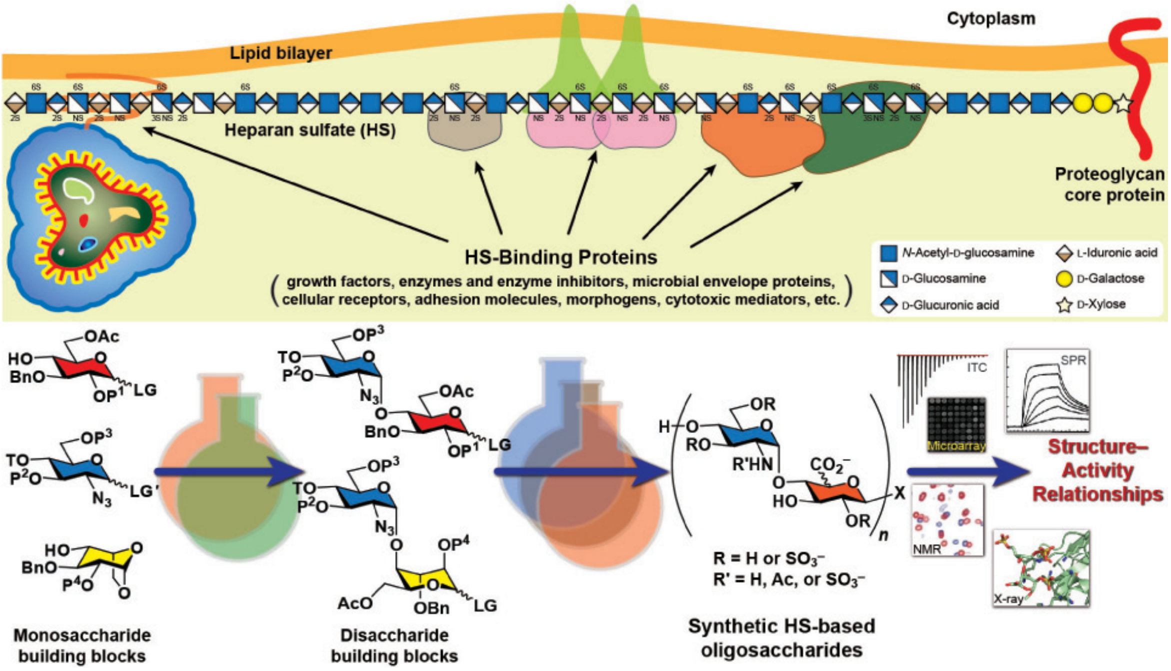
Research Interests

Carbohydrate Synthesis, Glycotechnology, and Glycobiology

Dr. Hung’s group aims on the development of “regioselective one-pot protection” and “stereoselective one-pot glycosylation” strategies to synthesize biologically potent oligosaccharides for the studies of infectious diseases and cancer. The major interests include three topics:

- Discovery of new technologies for carbohydrate synthesis
- Synthesis of cell surface carbohydrates and mycobacterial cell envelope components
- Investigation of cell surface heparan sulfate-protein interaction

- 發展醣的新合成技術
- 合成細胞表面醣體和結核桿菌細胞壁單元
- 探討細胞表面肝素寡醣和蛋白質的作用關係



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Education and Positions

- B. S. Chemistry, National Tsing Hua University, Taiwan, 1979
- M. S. Chemistry, The Johns Hopkins University, Baltimore, MD, 1986
- Ph.D. Chemistry, The Johns Hopkins University, Baltimore, MD, 1987
- Postdoctoral Research Associate, Department of Physics, University of Virginia, 1987-1988
- Postdoctoral Research Scientist, Department of Biochemistry and Molecular Biophysics, Columbia University, 1988-1991
- Associate Research Scientist, Department of Biochemistry and Molecular Biophysics, Columbia University, 1991-1997
- Research Scientist, Department of Biochemistry and Molecular Biophysics, Columbia University, 1997-2000
- Research Scientist, Columbia Genome Center, Genomics Informatics Section, Columbia University, 1999-2000
- Assistant Professor, Department of Pharmacology and Columbia Genome Center, Columbia University, 2000-2004
- Associate Research Fellow, Genomics Research Center, Academia Sinica, 2004-2010
- Research Fellow, Genomics Research Center, Academia Sinica, 2010-present

Honors

- Fellowship - William J. Matheson Foundation at Columbia University, 2000-2002

Selected Publications

- Yu, C. M.; Peng, H. P.; Chen, I. C.; Lee, Y. C.; Chen, J. B.; Tsai, K. C.; Chen, C. T.; Chang, J. Y.; Yang, E. W.; Hsu, P. C.; Jian, J. W.; Hsu, H. J.; Chang, H. J.; Hsu, W. L.; Huang, K. F.; Ma, C.; Yang, A. S., Rationalization and design of the complementarity determining region sequences in an antibody-antigen recognition interface. *PLoS ONE*, 2012, *7*, e33340.
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- Chang, H. J.; Yang, A. S., Design of phage-displayed cystine-stabilized mini-protein libraries for proteinaceous binder engineering. *Methods in Molecular Biology,* 2014, *1088*, 1-17.
- Hsu, H. J.; Lee, K. H.; Jian, J. W.; Chang, H. J.; Yu, C. M.; Lee, Y. C.; Chen, I. C.; Peng, H. P.; Wu, C. Y.; Huang, Y. F.; Shao, C. Y.; Chiu, K. P.; Yang, A. S., Antibody variable domain interface and framework sequence requirements for stability and function by high throughput experiments. *Structure*, 2014, *22*, 22-34.
- Hsu, H. J.; Yang, A. S., Substrate phage display for protease substrate sequence characterization: bovine factor Xa as a model system. *Methods in Molecular Biology*, 2014, *1088*, 107-24.
- Mahalingam, R.; Peng, H. P.; Yang, A. S., Prediction of FMN-binding residues with three-dimensional probability distributions of interacting atoms on protein surfaces. *Journal of Theoretical Biology*, 2014, *343*, 154-61.
- Peng, H. P.; Lee, K. H.; Jian, J. W.; Yang, A. S., Origins of specificity and affinity in antibody-protein interactions. *PNAS*, 2014, *111*, E2656-65.
- Mahalingam, R.; Peng, H. P.; Yang, A. S., Prediction of fatty acid-binding residues on protein surfaces with three-dimensional probability distributions of interacting atoms. *Biophysical Chemistry*, 2014, *192*, 10-9.

Research Interests

The research direction in this laboratory is to engineer proteins of significant biomedical importance. We develop computational and bioinformatic approaches to design stable protein scaffolds and use phage-based molecular evolution to engineer stability in folding and affinity toward target molecules. The goal is to enhance the insight into molecular basis on protein recognition and to use the engineered proteins in biomedical applications. Specific areas of interest include: computational protein design, recombinant antibody engineering, protein-protein interaction, computational structural biology, structural bioinformatics, phage display of antibody libraries, synthetic antibody fragment library construction.

本實驗室主要的研究方向為蛋白質分子的設計與應用。利用計算生物學與生物資訊技術設計穩定的蛋白質分子，再藉由噬菌體表達技術，篩選具有高度穩定性與專一性功能的蛋白質分子，目的在於加深對蛋白質分子間交互作用的認知及在生物技術上的應用。研究的領域包括蛋白質設計、抗體工程、蛋白質交互作用、計算結構生物、結構生物資訊、噬菌體表達抗體庫、合成抗體庫建構。

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Education and Positions

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- Postdoctoral Fellow, Dept. of Molecular Biology & Biochemistry, University of California, Irvine, USA, 2004-2006
- Postdoctoral Fellow, Genomics Research Center, Academia Sinica, Taiwan, 2006-2007
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, Taiwan, 2007-2014
- Associate Research Fellow, Genomics Research Center, Academia Sinica, Taiwan, 2014-present

Honors

- Taiwan Dementia Society, LiFu Medical Research Foundation Academic Award, Advisor of the 2nd Price, 2011, and 1st Price, 2012
- The Taiwan Society for Biochemistry and Molecular Biology Traveling Fellowship, 2012
- Young Investigator Award, Biophysical Society of R.O.C., 2013
- Promising Women in Science Award, Wu Chieh Shiung Education Foundation, 2014

Selected Publications

- Ni, C.-L.; Shi, H.-P.; Yu, H.-M.; Chang, Y.-C.; Chen, Y.-R., Folding stability of amyloid-β40 monomer is an important determinant of the nucleation kinetics in fibrillization. *FASEB J*, 2011, *25*, 1390-401.
- Chen, W.-T.; Liao, Y.-H.; Yu, H.-M.; Cheng, I. H.; Chen, Y.-R., Distinct effects of Zn^{2+}, Cu^{2+}, Fe^{3+}, and Al^{3+} on amyloid-β stability, oligomerization, and aggregation: amyloid-β destabilization promotes annular protofibril formation. *J Biol Chem*, 2011, *286*, 9646-56.
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- Chang, Y.-J.; Chen, Y.-R., The co-existence of an equal amount of Alzheimer's amyloid-β 40 and 42 forms structurally stable and toxic oligomers through a distinct pathway. *FEBS J*, 2014, *281*, 2674-2687.
- Fang, Y.-S.; Tsai, K.-J.; Chang, Y.-J.; Kao, P., Woods, R.; Kuo, P.-H.; Wu, C.-C.; Liao, J.-Y.; Chou, C.-H.; Lin, V.; Jin, L.-W.; Yuan, H.; Cheng, I.; Tu, P.-H.; Chen, Y.-R.. Full-Length TDP-43 Forms Toxic Amyloid Oligomers that are Present in Frontotemporal Lobar Dementia-TDP Patients. Nature Communications, 2014, in press.

Research Interests

Protein Folding/Misfolding, Amyloids, and Neurodegenerative Diseases

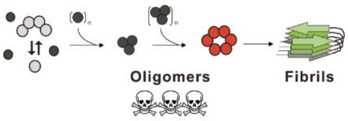
Our long-term research goal is to elucidate the underlying mechanisms of amyloidosis in the aspects of protein folding/structure and protein-protein interactions, and relate the results to the medical consequences. We utilize the knowledge to develop novel diagnostic means and therapeutic modalities. Currently, we are focusing on neurodegenerative diseases including *Alzheimer's disease (AD), Parkinson's disease (PD), and frontotemporal lobar dementia* (FTLD-U) and *amyotrophic lateral sclerosis* (ALS). We are working on several amyloid and amyloid-like proteins and their interacting partners in neurodegenerative diseases. They are amyloid-β (Aβ) peptide and tau, the major substance in senile plaques and tangles in the brain of AD, α-synuclein, the component of Lewy bodies in PD, and TDP-43, a novel inclusion found in a subtype of *frontotemporal lobar dementia* (FTLD-U) and *amyotrophic lateral sclerosis* (ALS). The major research interests are listed as follows:

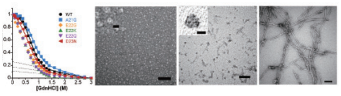
- Protein folding and misfolding of amyloids in neurodegenerative diseases.
- Amyloid protein oligomerization and the toxicity mechanisms in neurodegenerative diseases.
- Biomolecules involved in pathogenesis of the neurodegenerative diseases.
- Drug screening, diagnostic, and therapeutic developments in neurodegenerative diseases.

蛋白質錯誤摺疊及類澱粉蛋白疾病致病機轉

我們的研究重點在了解蛋白質摺疊與錯誤摺疊之類澱粉沉積症的致病機轉。類澱粉沉積症多與神經退化疾病相關，其中阿茲海默症為本世紀全球及臺灣日趨嚴重的疾病。我們將從了解致病蛋白堆積物的功能及機制，進而發展其診斷與治療的新方向。目前我們的研究著重於下列類澱粉及似類澱粉蛋白及其作用分子：(1) 阿茲海默症病人腦部老年斑塊的主要組成：類澱粉乙形蛋白 (amyloid-β) 及神經纖維糾結的主要組成 (tau)、(2) 帕金森氏症病人腦部路易士體的主要組成 α-synuclein、及 (3) 前側額顳葉失憶 / 肌萎縮側索硬化症中病癥的 TDP-43 蛋白。我們主要的研究目標如下：

- 蛋白質在神經退化疾病中的摺疊與錯誤摺疊機制
- 類澱粉蛋白寡聚體化及在神經退化疾病中引發之毒性機制
- 與病理相關生物分子在神經退化疾病中的作用
- 針對神經退化疾病發展藥物篩選、診斷及治療策略





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Education and Positions

- B.S., Chemistry, National Cheng-Kung University, Taiwan, 1991
- M.S., Chemistry National Tsing-Hua University, Taiwan, 1993
- Ph D., Chemistry, University of California, Davis CA, USA, 1997-2002
- Postdoctoral Fellow, the Scripps Research Institute, USA, 2002-2004
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, Taiwan, 2004-2010
- Associate Research Fellow, Genomics Research Center, Academia Sinica, Taiwan, 2010-present

Honors

- Skaggs Postdoctoral Fellowship, USA, 2002-2004
- The distinguished lectureship award (Natural products synthesis), the CSJ (Chemical Society of Japan) Asian International Symposium, Japan, 2007

Selected Publications

- Chan, T.-H.; Chang, Y.-F.; Hsu, J.-J.; Cheng, W.-C., Straightforward synthesis of diverse 1-deoxyazapyranosides via stereocontrolled nucleophilic additions to six-membered cyclic nitrones. *Eur J Org Chem*, 2010, *29*, 5555-9.
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- Cheng, W.-C.; Weng, C.-Y.; Yun, W.-Y.; Chang, S.-Y.; Lin, Y.-C.; Tsai, F.-J.; Huang, F.-Y.; Chen, Y.-R., Rapid modifications of *N*-substitution in iminosugars: development of new β-glucocerebrosidase inhibitors and pharmacological chaperones for Gaucher disease. *Bioorg Med Chem*, 2013, *21*, 5021-8.
- Chen K.-T.; Kuan Y.-C.; Fu W.-C.; Liang P.-H.; Cheng T.-J. R.; Wong C.-H.; Cheng W.-C., Rapid preparation of mycobacterium *N*-glycolyl Lipid I and Lipid II derivatives: a biocatalytic approach. *Chem Eur J*, 2013, *19*, 834-8.
- Pan Y.-W.; Guo C.-W.; Tu H.-Y.; Tsai C.-W.; Cheng W.-C., Solid-phase synthesis of diverse spiroisoxazolinodiketopiperazines. *ACS Comb Sci*, 2013, *15*, 425-34.
- Cheng, T.-J.; Chan, T.-H.; Tsou, E.-L.; Chang, S.-Y.; Yun, W.-Y.; Yang, P.-J.; Wu, Y.-T.; Cheng, W.-C., From natural product-inspired pyrrolidine scaffolds to the development of new human Golgi α-mannosidase II inhibitors. *Chem Asian J*, 2013, *8*, 2600-4.

Research Interests

The major research efforts of our group are directed toward the development of new synthetic strategies for biologically interesting natural products and heterocyclics. To understand the relationships between small molecules and biological systems, combinatorial approaches are applied in our diverse molecule library synthesis (core diversity, substituent diversity, and configuration diversity) with the assistance of automated or semi-automated equipment. Research interests include: Organic chemistry, Synthetic methodology, Natural product and bioactive molecule synthesis, Matrix-supported organic synthesis, Combinatorial chemistry, Synthesis of new glycophospholipids, Synthesis and functional study of Novel iminosugar alkaloids, Natural product-like library synthesis, Synthesis of bacterial (mycobacterial) cell wall components, Development of new chemical probes for biological applications, Pathogen host interaction, New molecules for innate immune study, Bioorganic chemistry, Chemical biology, Small molecules as chemical chaperones for lysosomal storage diseases, Development of new antibiotics, and Drug discovery.

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Education and Positions

- Ph.D. training with Jerry Workman, The Pennsylvania State University, 1992-1996
- Postdoctoral Fellow, 1997-2000; Assistant Investigator, 2000-2006, National Health Research Institutes, Taiwan
- Assistant, 2006-2009, and Associate Research Fellow, 2009-present, Genomics Research Center, Academia Sinica, Taiwan
- Adjunct Assistant, 2006-2010, and Associate Professor, 2010-present, Institute of Molecular Medicine, College of Medicine, National Taiwan University, Taiwan

Honors

- 1st Prize, Departmental Research Poster Award (1/76), The Penn State University, 1995
- 1st NHRI Postdoctoral Fellowship Competition Award (3/40), 1998
- Asia-Pacific International Molecular Biology Network (A-IMBN) Feature Report, 2008
- Academia Sinica Major Discovery, 2008
- Academia Sinica Career Development Award, 2009
- 4th TienTe Lee Biomedical Foundation Young Scientist Research Award, 2009
- Asia-Pacific International Molecular Biology Network (A-IMBN) Feature Report, 2010
- Best 5 Article in Cell Reports, 2012

Selected Publications

- Hsu, C.-H.; Chang, M. D. T.; Tai, K.-Y.; Yang, Y.-T.; Wang, P.-S.; Chen, C.-J.; Wang, Y.-H.; Lee, S.-C.; Wu, C.-W.; Juan, L.-J., HCMV IE2-mediated inhibition of HAT activity downregulates p53 function. *EMBO J* 2004, *23*, 2269-80.
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- Hsu, C.-H.; Peng, K.-L.; Jhang, H.-C.; Lin, C.-H.; Wu, S.-Y.; Chiang, C.-M.; Lee, S.-C.; Yu, W.-C.; Juan, L.-J.; The HPV E6 oncoprotein targets histone methyltransferases for modulating specific gene transcription. *Oncogene*, 2012, *31*, 2335-49.
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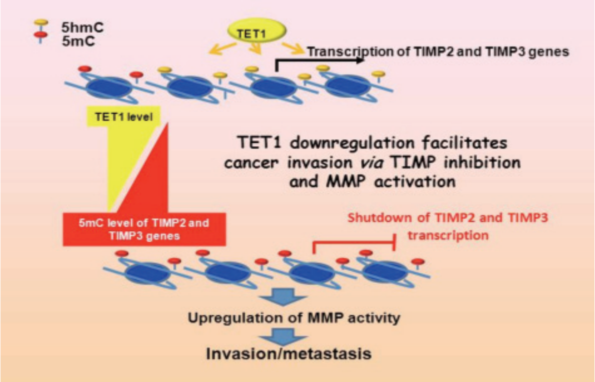
- Chu, C.-S.; Lo, P.-W.; Yeh, Y.-H,; Hsu, P.-H.; Peng, S.-H.; Teng, Y.-C.; Kang, M.-L.; Wong, C.-H.; Juan, L.-J.; O-GlcNAcylation regulates EZH2 protein stability and function. *Proc Natl Acad Sci USA*, 2014, *111*, 1355-60.

Research Interests

Epigenetic and Epigenetic Alterations Leading to Cancer

- hNaa10p in development and cancer
- DNA demethylases in cancer
- Glycosylation and epigenetics



DNA demethylase TET1 suppresses cancer invasion via activating the tissue inhibitors of metalloproteinases

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Education and Positions

- Ph.D., Chemistry, University of Cambridge, UK, 2000-2003
- Postdoctoral Fellow, Chemistry, University of Cambridge, UK, 2004
- Assistant Professor, National Taiwan Ocean University, 2004-2007
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, 2007-2011
- Associate Research Fellow, Genomics Research Center, Academia Sinica, 2011-present

Honors

- National Professionals and Technologists Certificate in Nutrition, Examination Yuan, 1991
- National Professional Certificate in Nutrition, Department of Health, 1991
- National Senior Civil Service Certificate in Environmental Hygiene, Examination Yuan, 1991
- Researcher Award, Annual Research Award, Department of Health, 1996
- Researcher Award, National Annual Research Award, Executive Yuan, 1997
- National Advanced Senior Civil Service Certificate in Hygiene Analysis, Examination Yuan, 1998
- Overseas PhD Fellowship in Chemistry, Minister of Education, 1998
- Career Development Awards, National Health Research Institutes, 2012-2015 & Academia Sinica, 2014-2018

Selected Publications

- Li, T. L.; Choroba, O. W.; Hong, H.; Williams, D. H.; Spencer, J. B., Biosynthesis of the vancomycin group of antibiotics: characterisation of a type III polyketide synthase in the pathway to (S)-3,5-dihydroxyphenylglycine. *Chem Commun*, 2001, 1752-3.
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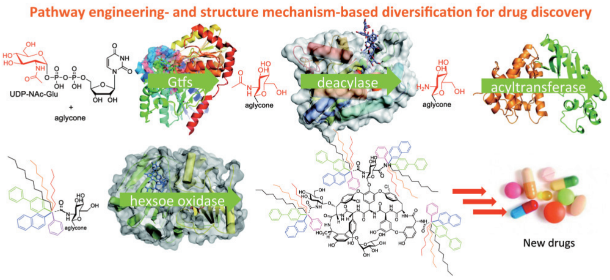
Research Interests

Chemical Biology and Drug Discovery

Research in the Li lab encompasses a broad spectrum of natural product chemistry particularly in the scopes of elucidation and manipulation of biosynthetic pathways to vital natural products. Natural product chemistry had its genesis in the study of naturally occurring substances, and this remains intellectual challenge despite a constant source of information. Molecular biology, structural biology, enzymology, organic chemistry, synthetic biology etc. are employed as study tools for drug discovery. Current targets include glycopeptides, aminoglycosides, and marine toxins.

我們的研究工作主要著重於天然產物化學，特別是對於天然產物生合成路徑的闡釋。我們運用分子生物學、基因工程、結構生物學、酵素學、有機合成、合成生物學作為研究工具嘗試開發出更具生理效能的藥物。目前研究的重點天然產物包含：醣胜肽類藥物，氨基糖類藥物及海洋毒素等。



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Education and Positions

- B.S., Chemistry, National Taiwan University, Taiwan, 1992
- Ph.D., Chemistry, University of Pennsylvania, USA, 2000
- Postdoctoral Fellow, The Scripps Research Institute, USA, 2001-2004
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, Taiwan, 2004-2010
- Associate Research Fellow, Genomics Research Center, Academia Sinica, Taiwan 2010-present

Honors

- The Skaggs Postdoctoral Fellowship, 2001-2003
- TWAS Young Affiliate, 2009-2013
- Academia Sinica Research Award for Junior Research Investigators, 2010
- The Young Scholar Award of TienTe Li Biomedical Foundation, 2011
- Academia Sinica Career Development Award, 2013
- Taiwan Bio-Development Foundation Chair in Biotechnology, 2014
- Taiwan Rotary Educational Foundation, Exceptional Merit in Academic Award, 2014

Selected Publications

- Ma, C.; Opella, S. J., Lanthanide ions bind specifically to an added "EF-hand" and orient a membrane protein in micelles for solution NMR spectroscopy. *J Magn Reson*, 2000, *146*, 381-4.
- Ma, C.; Marassi, F. M.; Jones, D. H.; Straus, S. K.; Bour, S.; Strebel, K.; Schubert, U.; Oblatt-Montal, M.; Montal, M.; Opella, S. J., Expression, purification, and activities of full-length and truncated versions of the integral membrane protein Vpu from HIV-1. *Protein Sci*, 2002, *11*, 546-57.
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- Sung, M. T.; Lai, Y. T.; Huang, C. Y.; Chou, L. Y.; Shih, H. W.; Cheng, W. C.; Wong, C. H.; Ma, C., Crystal structure of the membrane-bound bifunctional transglycosylase PBP1b from Escherichia coli. *Proc Natl Acad Sci USA*, 2009, *106*, 8824-9.
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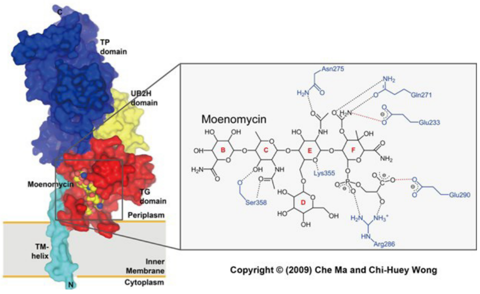
Research Interests

Structure of membrane proteins in drug discovery

The main focus of our laboratory is to study the structure and function of human-disease related membrane proteins, aiming to apply the obtained knowledge in drug discovery. Major efforts have been made in the two topics in infectious diseases. First, in order to overcome the current problems of drug-resistant bacterial infection, a new enzyme target for antibiotic development, the membrane-bound transglycosylase, has been chosen for structural and functional analysis. X-ray crystal structures of this membrane-bound enzyme in complex with its inhibitor moenomycin and the substrate lipid II analog have been determined, and the enzymatic mechanism of cell-wall peptidoglycan synthesis elucidated. In addition, a high-throughput screening method for finding new inhibitors against this enzyme has been developed using the purified full-length transglycosylase. Second, we have studied the effect of glycosylation on influenza virus major surface glycoprotein hemagglutinin (HA) with regards to its role in receptor binding and immune response, and discovered a new strategy for molecular vaccine design. Our research direction in the coming years will be a continued effort not only on the infectious diseases of drug-resistant bacterial infection and influenza vaccine, but also toward understanding the structure and function of membrane proteins in cancers. The goals are: (1) to use the crystal structures of transglycosylase in complex with inhibitors and substrates as a guide for structure-based antibiotic design; (2) to develop monoglycosylated hemagglutinin as a molecular vaccine against influenza, and (3) to determine the structural basis for the receptor sharing by interleukin cytokines in cancer cells and to use the structural information to devise therapeutic strategy for cancer treatment.



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Structure of PBP1b-moenomycin complex provides critical information for new antibiotic development.

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Education and Positions

- Ph.D., Applie d Chemistry, National Chiao-Tung University, 2000
- Postdoctoral Fellow, Institute of Chemistry, Academia Sinica, 2002-2004
- Postdoctoral Fellow, Genomics Research Center, Academia Sinica, 2004-2006
- Postdoctoral Fellow, Department of Chemistry, The Scripps Research Institute, 2004-2006
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, 2006-2011
- Associate Research Fellow, Genomics Research Center, Academia Sinica, 2011-present
- Chair Professor, Taiwan Bio-Development Foundation, 2014-present

Honors

- Project for Excellent Junior Research Investigators Award, National Science Council, Taiwan, 2012
- Career Development Award, Academia Sinica, Taiwan, 2012
- Academia Sinica Research Award for Junior Research Investigators, 2012
- Outstanding Alumni, Department of Applied Chemistry, National Chiao-Tung University, 2014
- The David Y. Gin New Investigator Award, American Chemical Society, 2014
- TBF Chair in Biotechnology Award, Taiwan Bio-Development Foundation, 2014

Selected Publications

- Chang, S.-H.; Han, J.-L.; Tseng, S.-Y.; Lee, H.-Y.; Lin, C.-W.; Lin, Y.-C.; Jeng, W.-Y.; Wang, A. H.; Wu, C.-Y.; Wong, C.-H., Glycan array on aluminum oxide-coated glass slides through phosphonate chemistry. *J Am Chem Soc*, 2010, *132*, 13371-80.
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- Shivatare, S. S.; Chang, S.-H.; Tsai, T.-I.; Ren, C.-T.; Chuang, H.-Y.; Hsu, L.; Wu, C.-Y.; Wong, C.-H., Efficient convergent synthesis of bi-, tri-, and tetraantennary complex type N-glycans and their HIV-1 antigenecity. *J Am Chem Soc*, 2013, *135*, 15382-91.
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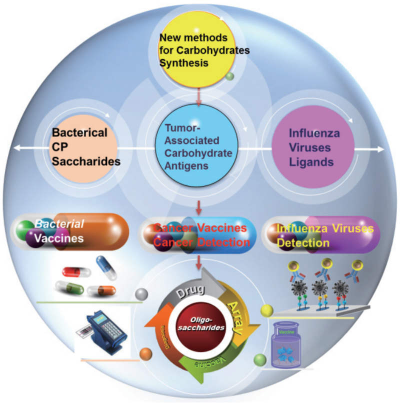
- Wu, C.-S.; Yen, C.-J.; Chou, R.-H.; Wu, C.-Y.; Yu, Y.-L., Downregulation of microRNA-15b by hepatitis B virus X enhances hepatocellular carcinoma proliferation via fucosyltransferase 2-induced Globo H expression. *Int J Cancer*, 2013, *7*, 1638-47.

Research Interests

Glycochemistry and Carbohydrate-Based Drug Discovery

More than 50% of human proteins are glycosylated. Glycomics has emerged with proteomics as an area for development and exploration in the postgenomic era. We focus on the development of novel and efficient methodologies to prepare biologically potent oligosaccharides and design the new type sugar array to elucidate the role of complex oligosaccharides involved in a host of biological processes of medical relevance. With the identification of diseases related carbohydrate. We can design glycan array for the detection of diseases or development of new therapeutic methods, including vaccines or drugs.

人類的蛋白質有超過一半以上都是被醣化修飾的醣蛋白。醣組學繼蛋白質體學後已被發展成後基因學時代瞭解疾病的重要學門。我們的研究重點主要著重在發展更新更快速的方法，用以製備與生理活性息息相關的醣分子，並用以設計出新型的醣晶片以了解這些醣分子所扮演的生理角色及其可能的藥物發展潛力。利用與疾病相關的醣分子我們可以設計醣晶片來作疾病的偵測或診斷，或是開發出新的疾病治療方法，包括疫苗及新的藥物開發。



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Education and Positions

- B.S., Agricultural chemistry, National Taiwan University, 1992
- M.S., Biotechnology, National Taiwan Ocean University, 1997
- Ph.D., Life Sciences, National Defense Medical Center, 2004
- Postdoctoral Associate, Weill Medical College, Cornell University, 2005-2011
- Research Associate, Weill Medical College, Cornell University, 2011
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, 2011-present

Honors

- Postdoctoral Fellowship, Cancer Research Institute, 2006-2009

Selected Publications

- Yin, Q.; Park, H. H.; Chung, J. Y.; Lin, S. C.; Lo, Y. C.; da Graca, L. S.; Jiang, X.; Wu, H., Caspase-9 holoenzyme is a specific and optimal procaspase-3 processing machine. *Mol Cell*, 2006, *22*, 259-68.
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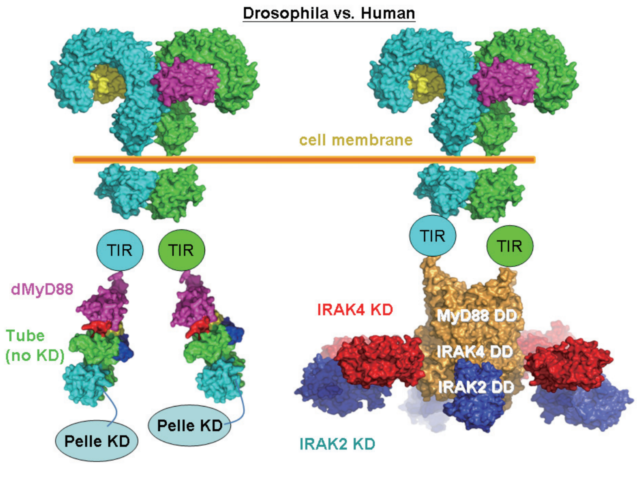
- Lin, S. C.; Lo, Y. C.; Wu, H., Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR/IL-1R signalling. *Nature*, 2010, *465*, 885-90.

Research Interests

Our future research goal is to unravel the signaling mechanisms in immune responses and cancers by structural and biochemical studies. Specifically, our goal is to better understand the signaling pathways that lead to or are involved in inflammatory diseases, which will help the development of therapies that could relieve the symptoms or treat the diseases. Our recent research effort has concentrated on the signaling complexes involved in TLR/IL-1R signaling that initiates innate immunity. One example is the death domain complex of MyD88:IRAK4:IRAK2. The complex has a unique helical assembly that control signaling leading to NF-kB activation.

本實驗室的研究工作主要放眼於了解免疫系統與癌症相關疾病的訊息傳遞機制，利用結構生物、生物化學、生物物理等技術來探討訊息傳遞蛋白的運作方式，最終目的是希望能有助於疾病治療法的開發與發展。



Toll-like receptor signaling complexes in Drosophila (left) and humans (right).

Medical Biology Division

This Division has focused on four major areas of translational medicine: 1) Cancer biology and therapeutics, 2) Stem cell biology and regenerative medicine, 3) Immunobiology and new biologics discovery, and 4) Molecular and genomic epidemiology. The ultimate goal is to develop new preventives, diagnostics and therapeutics with small molecules, biologics, and cell-based approaches. Many of the projects described below involve integrated efforts of GRC investigators within and across different Divisions. Through such concerted research endeavors, we hope to achieve the long term goal to elucidate the molecular mechanisms of genes and biomarkers associated with cancer and infection, develop targeted therapeutics and long-term risk calculators, and conduct translational researches to bridge the gap between scientific discovery and clinical medicine.

- **Cancer Biology and Therapeutics**

The main focus is on molecular biology of cancers as well as cancer immunotherapy and vaccine development. Key research projects include: 1) elucidation the interaction networks of retinoblastoma (RB) gene, which modulate RB suppressive activity, 2) identification of small molecules that disrupt the interaction between mitotic kinase Nek2 and RB-interaction protein Hec1 for cancer treatment, 3) identification of small molecules that disrupt the interaction between BRC repeat and Rad51, which may be used for new combinatory treatment with chemotherapy or radiotherapy, 4) elucidation the roles of microenvironment in breast and pancreatic tumorigenesis, 5) development of antibody against IL-17RB to block tumor metastasis, 6) elucidation of tumor growth/survival pathways to enhance tumor chemosensitivity or radiosensitivity, 7) development of nanoparticle-mediated high-throughput transfection platforms to identify and characterize novel gene expression, and 8) preclinical and clinical development of therapeutics targeting Globo H and SSEA4 epitopes of breast and pancreatic cancer.

- **Stem Cell Biology and Regenerative Medicine**

The main focus is using novel techniques including genomics, glycomics and proteomics to unravel somatic cell reprogramming and stem cell renewal and differentiation. Key research projects include: 1) Conversion (trans-differentiation) of cells of alternative resources to beta-cells, 2) Identification of key factors that modulate acinar cell reprogramming in pancreatitis, which may contribute to the development of pancreatic cancer, 3) delineation the role of reprogramming in pancreatic cancer stemness in order to develop strategies to target cancer stem cells, 4) identification of key factors for cell fate determination in mouse embryonic stem cells, human embryonic stem cells and mesenchymal stem cells using shRNA screening, 5) identification of genes essential and sufficient to promote osteogenesis of human embryonic stem cells, 6) elucidation of mechanisms underlying dentritic cell homeostasis, and 7) exploration of interactions between dentritic cell turnover and infectious agents and tumors.

- **Immunobiology and New Biologics Discovery**

The major focus is the elucidation of immune regulation and discovery of new drugs. Key research projects include: 1) investigation of pharmacological mechanisms of the anti-IgE antibody in various diseases, 2) development of antibodies specific for migis-α for the treatment of IgA nephropathy, 3) development of antibodies to target mIgE-expressing B cells for the treatment of IgE-mediated diseases, 4) identification of glycans-binding proteins critical for host-pathogen interaction and immunomodulation, 5) Development of antibodies as novel therapeutics for anti-inflammation, 6) elucidation of the mode of action of a master regulator of cell differentiation, Blimp-1, 7) elucidation of molecular mechanisms of tumorigenesis of plasma and mature B cells, and 8) elucidation of transcriptional regulation in dentritic cell development and maturation.

- **Molecular and Genomic Epidemiology**

The major focus is the identification of biomarkers and development of risk calculators of major infectious diseases and cancers. Key research projects include: 1) identification and validation of molecular and genomic biomarkers associated with chronic viral hepatitis, chronic arsenic poisoning, virus-related cancers, and female lung adenocarcinoma, 2) development of risk calculators for the prediction of long-term risk of chronic arsenic poisoning and chronic oncogenic viral infections, 3) elucidation of gene-environment and gene-gene interactions in the arsenic-caused health hazards and virus-caused cancers, 4) elucidation of immunological factors involved in progression of chronic viral hepatitis, and 5) development of genomic, proteomic and glycomic biosignatures to develop novel methods for early diagnosis and prevention of cancers.

醫學生物專題中心

醫學生物專題中心聚焦在四個主要的轉譯醫學領域： (1) 癌症生物學及治療藥物 (2) 幹細胞生物學和再生醫學 (3) 免疫生物學及抗體藥物研發 (4) 分子及基因體流行病學。主要的目標是發展和測試小分子藥物、抗體藥物和疫苗、以及免疫藥物來預防、診斷和治療疾病。本專題中心與其他專題中心有多項共同研究計畫，經由跨領域的合作，我們希望能達成的長期目標，是藉由闡明與癌症和傳染病相關的基因及生物標幟的分子機制，研發標靶性治療藥物及疾病長期風險預測，進行轉譯醫學研究以搭建科學研究發現與臨床醫學應用之間的橋樑。

• 癌症生物學與治療藥物

主要聚焦於癌症分子生物學與癌症治療藥物之研發。重要研究方向有 (1) 探索可以調控 RB 基因之抑癌活性的蛋白質互動網絡，(2) 發現可以抑制 Hec1 功能而達到抑癌效果的小分子藥物，(3) 發現可以阻礙 BRCA2/Rad51 複合體的形成而達到抑癌作用的小分子藥物，(4) 探討癌細胞與微環境之間的相互作用與分子機制，(5) 開發 IL17RB 之抗體藥物以治療 IL17RB/IL17B 過度表達的癌症，(6) 探討腫瘤成長 / 存活之路徑以增強腫瘤對化學 / 放射療法之敏感度，(7) 利用奈米顆粒發展高通量平台以探討癌細胞之新穎基因的表現，(8) 以 Globo H 及 SSEA4 為基礎進行臨床前及臨床試驗，研發乳癌及胰臟癌的治療方法。

• 幹細胞生物學與再生醫學

主要聚焦於利用基因體學、醣體學、蛋白體學的嶄新技術，探索體細胞重新編程以及幹細胞更新與分化。重要研究方向有 (1) 以糖尿病小鼠模式利用重新編程將組織細胞轉變功能胰島細胞，(2) 結合細胞重新編程或建構胰腺專一表達突變基因的標定鼠及原位胰臟癌小鼠，研究行胰臟癌化的機制，(3) 探討胰臟癌幹細胞是否來自特定細胞的重新編程，以開發新的胰臟癌治療策略，(4) 利用小鼠胚胎幹細胞，人類胚胎幹細胞，和間質幹細胞，進行 shRNA 篩選以探索決定細胞的命運的樞紐因子，(5) 發現成骨作用所必要的候選基因，這些基因的過度表達足以促進間質幹細胞的成骨作用，(6) 探索免疫樹突細胞的生存及更新的調控，(7) 闡明免疫樹突細胞的更新與感染病原及腫瘤的交互作用。

• 免疫生物學及抗體藥物研發

主要聚焦於免疫調控的探索與新穎抗體藥物的研發。重要研究方向有 (1) 研究 anti-IgE 抗體藥物在特殊疾病的藥理機制，(2) 發展對 migis-α 具結合特異性的抗體，以抑制表達膜 IgA 的 B 淋巴細胞，治療 IgA 腎疾，(3) 持續發展可標靶表現膜 IgE 的 B 淋巴細胞，以治療各種 IgE 所引發的疾病，(4) 分析與宿主—病原體相互作用以及免疫調節有關的聚醣接合蛋白，(5) 發展可以抗發炎的之抗體藥物，(6) 闡明細胞分化主要調控因子 Blimp-1 的作用機制，(7) 探索漿細胞與 B 細胞癌化的分子機制，(8) 研究免疫樹突細胞發育與成長的轉錄調控。

• 分子及基因體流行病學

主要聚焦於重要傳染病與癌症之生物標幟的辨明與長期風險的預測。重要研究方向有 (1) 發現與確認慢性病毒肝炎、慢性砷中毒、病毒誘發之癌症、女性肺腺癌的分子及基因體標幟，(2) 開發慢性砷中毒之健康效應以及病毒誘發之癌症的長期風險預測模式，(3) 闡明慢性砷中毒以及病毒誘發癌症機制中的基因 - 基因與基因 - 環境交互作用，(4) 利用高通量技術如全基因體研究、次世代定序、多重蛋白質檢測、以及醣晶片來探討宿主（免疫）因子在慢性病毒性肝炎、肝硬化及肝細胞癌所扮演的角色，(5) 利用發病前生物檢體，探索主要癌症發生前之基因體、蛋白質體、以及醣體生物標幟，以研發癌症之預防疫苗及早期診斷工具。

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Education and Positions

- Sc.D., Department of Epidemiology, Johns Hopkins University, 1982
- Professor, National Taiwan University College of Public Health, 1986-present
- Director, Graduate Institute of Public Health, National Taiwan University, 1993-1994
- Director, Graduate Institute of Epidemiology, National Taiwan University, 1994-1997
- Director General, Division of Life Sciences, National Science Council, ROC, 1997-1999
- Dean, College of Public Health, National Taiwan University, 1999-2002
- Deputy Minister, National Science Council, ROC, 2002-2003
- Minister, Department of Health, ROC, 2003-2005
- Minister, National Science Council, ROC, 2006-2008
- Distinguished Research Fellow, Genomics Research Center, Academia Sinica, 2006-present

Honors

- Scholarship for Studying Abroad, Ministry of Education, 1979
- Outstanding Research Award, National Science Council, ROC, 1986-1996
- Fogarty International Research Fellowship, US National Institute of Health, 1989
- Outstanding Teaching Award, Ministry of Education, ROC, 1992
- Outstanding Scholar, Foundation for Outstanding Scholarship, 1995-1999
- Academic Award, Ministry of Education, ROC, 1997
- Academician, Academia Sinica, 1998
- Outstanding Anti-Cancer Research Award, Taiwan Cancer Foundation, 1999
- National Chair Professor, Ministry of Education, ROC, 1997-2002
- ISI Citation Classic Award, ISI Thomas Scientific, 2001
- Outstanding Research Fellow Award, National Science Council, ROC, 2003
- Health Medal (First Rank), Department of Health, ROC, 2005
- Achievement Medal (First Rank), Executive Yuan, ROC, 2005
- Presidential Science Prize, ROC, 2005
- Member, World Academy of Sciences, 2005
- Honorary Member, Mongolian Academy of Sciences, 2007
- Cutter Lecturer on Preventive Medicine, Harvard University, 2008
- Dr. D. V. Datta Memorial Oration, Indian National Association for Study of the Liver, 2008
- Officier dans l’Ordre des Palmes Academiques, Ministry of Education, France, 2009
- Science and Engineering Achievement Award, Taiwanese-American Foundation, USA, 2009
- Member, Delta Omega Honorary Society in Public Health, Johns Hopkins University, 2010
- Outstanding Merit Award, Wang Ming-Ning Memorial Foundation, Taiwan, 2010
- 14th Prof. Vikit Viranuvatti Lecturer, Gastroenterological Association of Thailand, 2011
- Science Profession Medal (First Rank), National Science Council, ROC, 2012
- Knowledge for the World Award, Johns Hopkins University, 2012
- Knight, Pontifical Equestrian Order of St. Gregory the Great, Vatican, 2013
- Outstanding Contribution in Science and Technology Award, Executive Yuan, Taiwan, 2013

Selected Publications

- Chen, C. J.; Chuang, Y. C.; Lin, T. M.; Wu, H. Y., Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: High-arsenic artesian well water and cancers. *Cancer Res*, 1985, *45*, 5895-9.
- Chen, C. J.; Chen, C. W.; Wu, M. M.; Kuo, T. L., Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. *Brit J Cancer*, 1992, *66*, 888-92.
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- Chien, Y. C.; Chen, J. Y.; Liu, M. Y.; Yang, H. I.; Hsu, M. M.; Chen, C. J.; Yang, C. S., Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. *New Engl J Med*, 2001, *345*, 1877-82.
- Yang, H. I.; Lu, S. N.; You, S. L.; Sun, C. A.; Wang, L. Y.; Hsiao, K.; Chen, P. J.; Chen, D. S.; Liaw, Y. F.; Chen, C. J., Hepatitis B e antigens and the risk of hepatocellular carcinoma. *New Engl J Med*, 2002, *347*, 168-74.
- Chen, C. L.; Hsu, L. I.; Chiou, H. Y.; Hsueh, Y. M.; Chen, S. Y.; Wu, M. M.; Chen, C. J.. Ingested arsenic, cigarette smoking and lung cancer risk: A follow-up study in arseniasis-endemic areas in Taiwan. *JAMA*, 2004, *292*, 2984-90.
- Chen, C. J.; Yang, H. I.; Su, J.; Jen, C. L.; You, S. L.; Lu, S. N.; Huang, G. T.; Iloeje. U. H., Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*, 2006, *295*, 65-73.
- Iloeje, U. H.; Yang, H. I.; Su, J.; Jen, C. L.; You, S. L.; Chen, C. J.; Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology*, 2006, *130*, 678-86.
- Yang, H. I.; Yuen, M. F.; Chan, H. L.; Han, K. H.; Chen, P. J.; Kim, D. Y.; Ahn, S. H.; Chen, C. J.; Wong, V. W.; Seto, W. K., Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol*, 2011, *12*, 568-574.
- Chiang, C. J.; Yang, Y. W.; You, S. L.; Lai, M. S.; Chen, C. J., Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. *JAMA*, 2013, *310*, 974-6.

Research Interests

Molecular and genomic epidemiology

- Identification and validation of biomarkers associated with chronic arsenic poisoning, hepatocellular carcinoma, cervical carcinoma, nasopharyngeal carcinoma and female lung adenocarcinoma.
- Development of risk calculators for the prediction of long-term health risk of chronic arsenic poisoning and chronic infection of hepatitis B and C virus, human papillomavirus and Epstein-Barr virus, respectively
- Identification and validation of genetic susceptibility to arsenic-induced health hazards, hepatocellular carcinoma, cervical carcinoma, nasopharyngeal carcinoma, and female lung adenocarcinoma.

我們的工作主要著重於慢性砷中毒與病毒致癌的分子及基因體流行病學研究，包括：

- B 型及 C 型肝炎病毒誘發肝細胞癌的長期追蹤研究與風險評估；
- 人類乳突病毒誘發子宮頸癌的長期追蹤研究與風險評估；
- Epstein-Barr 病毒誘發鼻咽癌的長期追蹤研究與風險評估；
- 慢性砷中毒誘發多重健康危害的分子流行病學研究 : 遺傳與環境交互作用分析；
- 女性肺腺癌的基因體流行病學研究 : 基因 - 基因與基因 - 環境交互作用的分析。

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Education and Positions

- Ph.D., Cell and Developmental Biology, Harvard University, 1977
- Postdoctoral Fellow, Massachusetts Institute of Technology, 1977-1980
- Department Supervisor, Cellular Immunology, Ortho Pharmaceutical Corp, 1980-1981
- Director of Immunology to V.P. of Research, Centocor, Inc., 1981-1985
- Professor, Division of Molecular Virology, Baylor College of Medicine, 1986-1991
- Cofounder, V.P. of R & D, Director, Tanox, Inc. 1986-2007
- Professor, Dean, Tsing Hua Professor of Life Science, College of Life Science, 1996-2006
- President, Development Center for Biotechnology, 2003-2006
- Distinguished Research Fellow, Genomics Research Center, Academia Sinica, 2006-present

Honors

- Appointed Science and Technology Advisor of the Executive Yuan, 2002-2006
- Xolair approved by FDA, USA for adults and adolescents with moderate to severe asthma, 2003
- Xolair chosen for “Immunology Molecule of the Year” Award by Pharmaward USA, 2004
- Honorary Fellow Award from American College of Asthma, Allergy, and Immunology, 2004
- Nature Biotechnology’s shortlist of personalities who made the most significant contribution to biotech in the past 10 years, 2006
- Xolair chosen for Prix Galien Award for Outstanding Innovation in R&D, UK, 2006
- Honorary Fellow Award from American Academy of Asthma, Allergy and Immunology, 2007
- “Father of Xolair” plaque from Novartis, in Middle East Asthma and Allergy Conference, 2012
- “Lifetime Achievement Award in Allergy” from Taiwan Academy of Pediatric Allergy Asthma and Clinical Immunology, 2013

Selected Publications

- Chang, T. W., Pharmacological basis of anti-IgE therapy. *Nat Biotechnol*, 2000, *18*, 157-62.
- Chang, T. W.; Shiung, Y. Y., Anti-IgE as a mast cell-stabilizing therapeutic agent. *J Allergy Clin Immunol*, 2006, *117*, 1203-12.
- Chang, T. W.; Wu, P. C.; Hsu, C. L.; Hung, A. F., Anti-IgE antibodies for the treatment of IgE-mediated allergic diseases. *Adv Immunol*, 2007, *93*, 63-119.
- Chang, T. W.; Pan, A. E., Cumulative environmental changes, skewed antigen exposure, and the increase of allergy. *Adv Immunol*, 2008, *98*, 39-84.
- Chen, J. B.; Wu, P. C.; Hung, A. F. H.; Chu, C. Y.; Tsai, T. F.; Yu, H. M.; Chang, H. Y.; Chang, T. W., Unique epitopes on CεmX in IgE-BCR are potentially applicable for targeting IgE-committed B cells. *J Immunol*, 2010, *184*, 1748-56.
- Chang, T. W.; Chen, J. B.; Chu, C. Y., The pharmacological mechanisms of omalizumab in patients with very high IgE levels - clues from studies on atopic dermatitis. *Dermatol Sin*, 2012, *30*, 147-53.
- Lin, C. J.; Chen, N. Y.; Chen, J. B.; Lu, C. S.; Hung, A. F.; Shiung, Y. Y.; Wu., P. C.; Pan, R. L.; Chang, T. W., CεmX peptide-carrying HBcAg virus-like particles induced antibodies that down-regulate mIgE-B lymphocytes. *Mol Immunol*, 2012, *52*, 190-9.
- Wu, P. C.; Chen, J. B.; Kawamura, S.; Roos, C.; Merker. S.; Shih, C. C.; Hsu, B. D.; Lim, C.; Chang, T. W., The IgE gene in primates exhibits extraordinary evolutionary diversity. *Immunogenetics* 2012, *64*, 279-87.

- Chu, H. M.; Wright, J.; Chan, Y. H.; Lin, C. J.; Chang, T. W.; Lim, C., Two potential therapeutic antibodies bind to a peptide segment of membrane-bound IgE in different conformations. *Nat Commun*, 2014, *5*, 3139.
- Chang, T. W.; Chen, C.; Lin, C. J.; Metz, M.; Church, M. K.; Maurer, M., The potential pharmacological mechanisms of omalizumab in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*, 2014, e-published June 27.

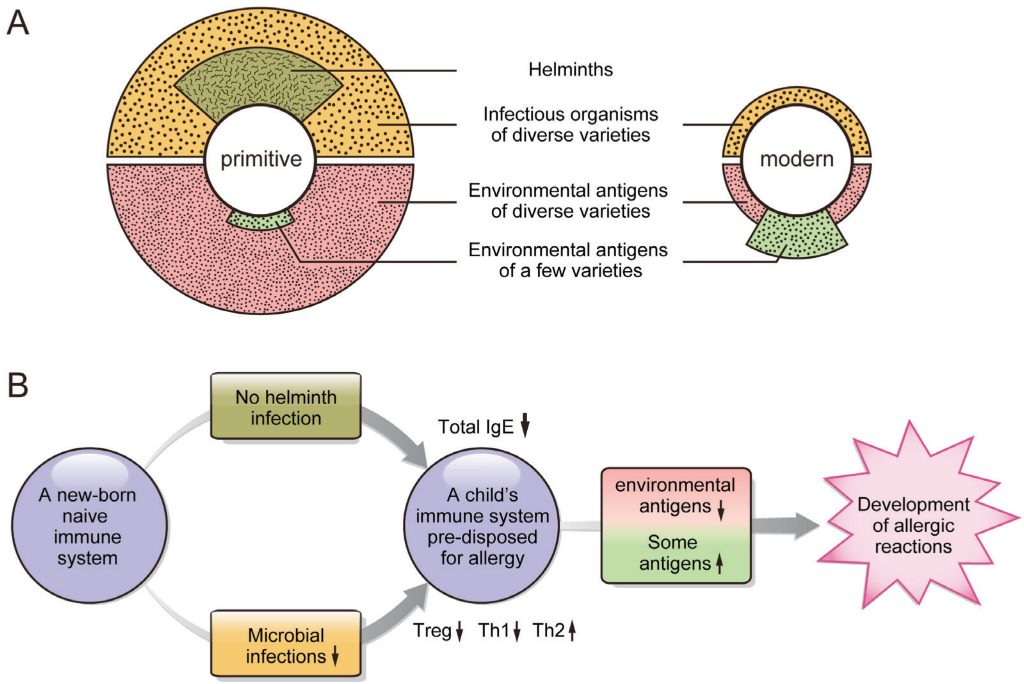
Research Interests

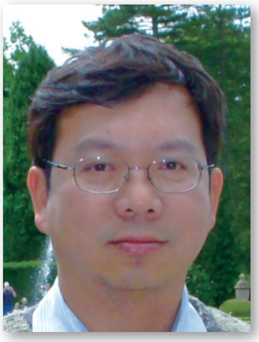
New drug discovery for treating diseases caused by abnormal immune regulation

- Clinical utilities of anti-IgE and anti-CεmX antibodies - To explore the applications based on the discoveries of anti-IgE and CεmX and to explain the pharmacologic mechanisms of anti-IgE and anti-CεmX in various allergic and skin inflammatory diseases
- Antibody new drug discovery - To develop a therapeutic antibody specific for migis-α epitope on membrane-bound IgA-expressing B lymphocytes as a potential treatment for IgA nephropathy
- Theory of why allergy is prevalent - To elucidate in-depth and obtain experimental evidence for “skewed antigen exposure theory” proposed by our group for the prevalence of allergy in modern societies

我們的研究著重於研發新藥以治療因免疫失調引致的疾病

- **Anti-IgE 及 anti-CεmX 抗體藥物的臨床應用** – 繼續與臨床醫師合作，發掘 anti-IgE 及 CεmX 的應用，並解析此兩種新藥在不同疾病的藥理機制。
- **抗體新藥研發** – 發展對表現膜 IgA 之 B 細胞表面的 migis-α 抗原部位具結合特異性的抗體新藥，以用來控制體內 IgA 的生產，達到治療 IgA 腎疾的效果。
- **解釋為何過敏疾病如此普遍** – 進一步解釋並取得實驗證據來支持本研究群提出的「抗原偏頗接觸」學說（見圖示），以更深入解釋過敏疾病在現代社會極為普遍的現象。





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Education and Positions

- M.D., National Yang-Ming University, Taiwan, 1984
- D.Phil., University of Oxford, UK, 1992
- Postdoctoral fellow, Stanford University, 1993
- Director, Immunology Research Center, National Yang-Ming University, Taiwan, 2000-2013
- Director, Immunology Research Center, Taipei Veterans' General Hospital, Taiwan, 2005-2013
- Department head, Department of Microbiology and Immunology, National Yang-Ming University, Taiwan, 2007-2013
- Director, Institute of Clinical Medicine, National Yang-Ming University, Taiwan, 2010-2013
- Adjunct Senior Investigator, National Health Research Center, Taiwan, 2004-present
- Adjunct Professor, Institute of Clinical Medicine, National Yang-Ming University, Taiwan, 2013-present
- Adjunct Research Fellow, Taipei Veterans' General Hospital, Taiwan, 2013-present
- Distinguished Research Fellow, Academia Sinica, Taipei, Taiwan, 2013-present

Honors

- Oversea PhD studentship from the Ministry of Education, Taiwan, 1989
- Oversea Research Scholarship (ORS) from the University of Oxford, 1989
- Irvington Medial Foundation post-doctoral fellowship 'Robert Wood Johnson Fellow, 1992
- Outstanding Researcher Award from the National Science Council, 1999, 2003, 2010
- Outstanding Alumni, National Yang-Ming University, 2003
- Outstanding research Achievement to National Health, Ming-Ning Wang Memorial Foundation, 2008
- Tsungming Tu Award, Taiwan Medical Society, 2009
- Long-Term Award from Acer Foundation, 2009
- Academic Achievement Award, Ministry of Education, 2009
- National Chair Professor Award, Ministry of Education, 2012
- TienTe Lee Award, 2013

Selected Publications

- Chang, Y. C.; Chan, Y, H.; Jackson, D. G.; Hsieh, S. L., The glycosaminoglycan-binding domain of decoy receptor 3 is essential for induction of monocyte adhesion. *J Immunol*, 2006, *176*, 173-80.
- You, R. I.; Chen, M. C.; Wang, H. W.; Chou, Y. C.; Lin, C. H.; Hsieh, S. L., Inhibition of lymphotoxin-beta receptor-mediated cell death by survivin-DeltaEx3. *Cancer Res*, 2006, *66*, 3051-61.
- Tang, C. H.; Hsu, T. L.; Lin, W. W.; Lai, M. Z.; Yang, R. S.; Hsieh, S. L,l Fu, W. M., Attenuation of bone mass and increase of osteoclast formation in decoy receptor 3 transgenic mice. *J Biol Chem*, 2007, *282*, 2346-54.
- Chen, S. T.; Lin, Y. L.; Huang, M. T.; Wu, M. F.; Cheng, S. C.; Lei, H. Y.; Lee, C. K.; Chiou, T, W.; Wong, C. H.; Hsieh, S. L., CLEC5A is critical for dengue virus-induced lethal disease. *Nature,* 2008, *453*, 672-5. FACULTY OF 1000-BIOLOGY (f1000 Factor 9.0-exceptional)
- Chang, Y. C.; Chen, T. C.; Lee, C. T.; Yang, C. Y.; Wang, H. W.; Wang, C. C.; Hsieh, S. L., Epigenetic control of MHC-II expression in tumor-associated macrophages by decoy receptor 3. *Blood,* 2008, *111*, 5054-63.
- You, R. I.; Chang, Y. C.; Chen, P. M.; Wang, W. S.; Hsu, T. L.; Yang, C. Y. Lee, C. T.; Hsieh, S. L., Apoptosis of dendritic cells induced by decoy receptor 3 (DcR3). *Blood*, 2008, *111*, 1480-8.

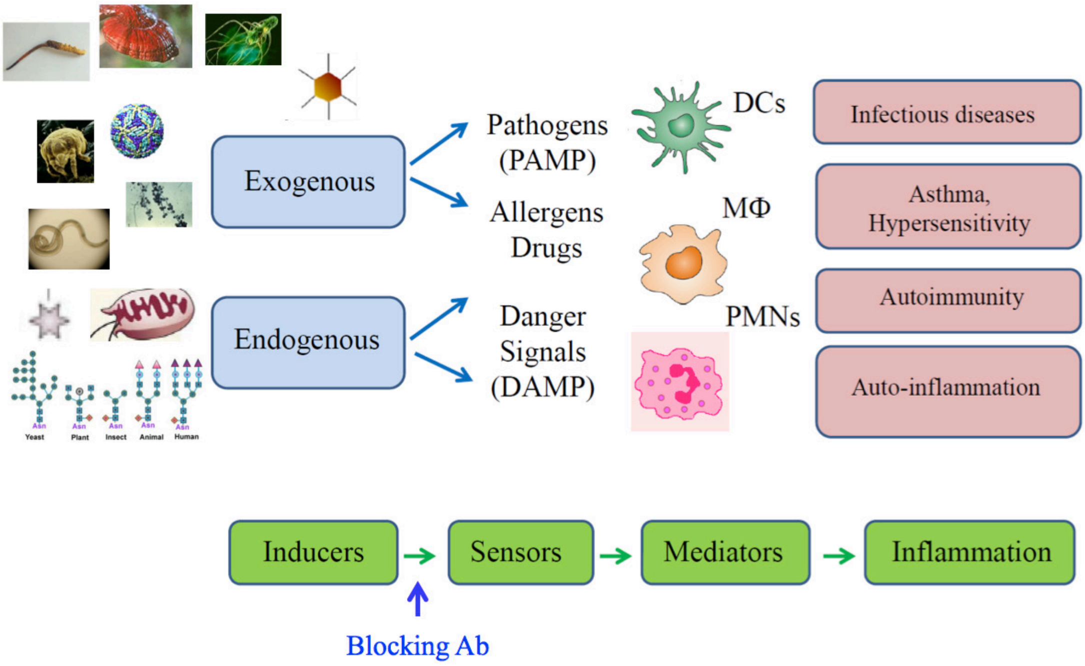
- Hsu, T. L.; Cheng, S. C.; Yang, W. B.; Chin, S. W.; Chen, B. H.; Huang, M. T.; Hsieh, S. L.; Wong, C. H., Profiling carbohydrate-receptor interaction with recombinant innate immunity receptor-Fc fusion proteins. *J Biol Chem*, 2009, 284, 34479-89.
- Chen, S. T.; Liu, R. S.; Wu, M. F.; Lin, Y. L.; Chen, S. Y.; Tan, D. T. W.; Chou, T. Y.; Tsai, I. S.; Li, L.; Hsieh, S. L., CLEC5A regulates Japanese encephalitis virus-induced neuroinflammation and lethality. *PLoS Pathog*, 2012, *8*, e1002655. FACULTY OF 1000 (f1000 Factor 8.0-must read)
- Wu, M. F.; Chen, S. T.; Yang, A. H.; Lin, W. W.; Lin, Y. L.; Chen, N. J.; Tsai, IS.; Li, L.; Hsieh, S. L.; CLEC5A modulates dengue virus-induced inflammasome activation in human macrophages. *Blood*, 2013, *121*, 95-106.
- Tung, Y. L.; Wu, M. F.; Wang, G. J.; Hsieh, S. L., Nanostructured electrochemical biosensor for the detection of the weak binding between the dengue virus and the CLEC5A receptor. *Nanomedicine*, 2014, in press.

Research Interests

Glycoimmunology

Research in the Hsieh lab encompasses the identification of glycans-binding proteins critical for host-pathogen interaction and immunomodulation, and production of monoclonal antibodies as potential novel therapeutic agents for anti-inflammation. New technology to detect weak interaction between glycans and lectins is developed to identify lectins receptors recognizing intact icosahedral virions, microparticles, microorganisms, and various glycoconjugates. Antagonistic bi-specific mAbs, and recombinant fusion proteins are being developed for immunomodulation to control aseptic and non-aseptic inflammatory diseases. Functions of novel polymorphic C-type lectins located in ER, Golgi and endosomes are being investigated systemically to reveal their impacts in the establishment of inflammatory reactions and human diseases.

我們實驗室的研究包括了分析與宿主及病原體相互作用與免疫調節有關的聚醣接合蛋白其功能、及生產當作抗免疫反應治療標的之單株抗體。目前也已發展可用來偵測聚醣與凝集素之間微弱相互作用的新技術，並可利用此技術來分析可與完整二十面體的病毒顆粒、微粒子、微生物及不同的醣接合物接合的凝集素接受器。具有雙特異性的拮抗抗體及重組的融合蛋白目前也已被發展來控制感染性及非感染性的發炎疾病等等免疫調節目地。至於位於內質體、高基氏體及核內體等處的 C 型凝集素也因為其在發炎反應及人類疾病的重要角色，而被驗證其具有特殊多樣的功能。



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Education and Positions

- B.S., Biology, National Taiwan Normal University, 1968-1972
- MS, Biochemistry, National Taiwan University, 1975-1977
- Ph.D., Molecular Biology, University of California at Berkeley, 1978-1981
- Postdoctoral, Molecular Biology, University of California at Berkeley, 1981-1982
- Research Scientist, Cetus Corporation at Berkeley, California, 1982-1983
- Visiting Scientist, Lawrence Berkeley Laboratory, Berkeley, 1983-1984
- Assistant Professor, Assoc. Professor, 1984-1990, Professor, 1990-1991, University of California at San Diego
- Professor/Chairman, Department of Molecular Medicine, Institute of Biotechnology, University of Texas Health Science Center at San Antonio, 1991-2003
- Member, NIH Cell Biology & Physiology Study Section II, 1992-1996
- Member, NCI Cancer Center Study Group IRG A, 1998-2002
- Donald Bren Professor, 2003-2013, Chairman, 2005-2008, Department of Biological Chemistry, University of CA at Irvine
- Distinguished Research Fellow, Genomics Research Center, Academia Sinica, 2012-present
- President, China Medical University (on secondment), 2014-present

Honors

- A.P. McDermott Distinguished University Professor, UTHSC-SA, 1991
- NIH Director Lectureship, 1991
- Outstanding Scientific Achievement, SCBA, 1992
- Alcon Research Award, 1994
- Elected Member, Sinica Academia, ROC, 1994
- F.E. Shideman-Sterling Award, Univ. of Minnesota, 1999
- Presidential Award, SCBA, 2001
- Outstanding Alumni Award, National Taiwan Normal University, 2002
- First Class Medal, Dept. of Health, Taiwan, 2002
- Inducted Member, Texas Hall of Fame for Science, Mathematics and Technology, 2003
- Donald Bren Chair Professorship, Univ. California , Irvine, 2003

Selected Publications

- Lee, W. H.; Shew, J. Y.; Hong, F. D.; Sery, T. W.; Donoso, L. A.; Young, L. J.; Bookstein, R.; Lee, E. Y., The retinoblastoma susceptibility gene encodes a nuclear phosphoprotein associated with DNA binding activity. *Nature*, 1987, *329*, 642-5.
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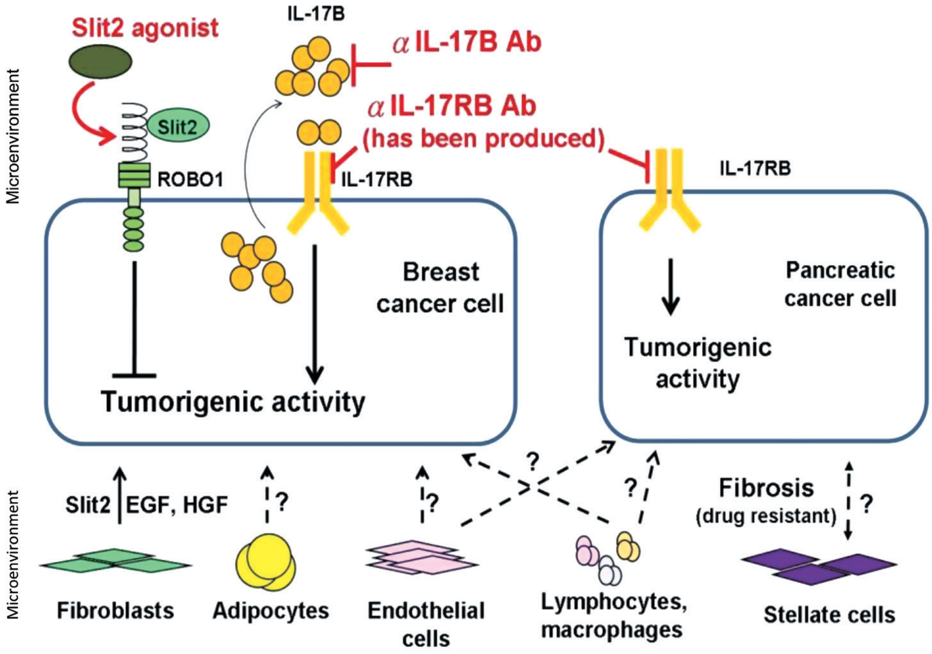
- Huang, C. K.; Yang, C. Y.; Jeng, Y. M.; Chen, C. L.; Wu, H. H.; Chang, Y. C.; Ma, C.; Kuo, W. H.; Chang, K. J.; Shew, J. Y.; Lee, W. H., Autocrine/paracrine mechanism of Interleukin-17B receptor promotes breast tumorigenesis through NF-κB-mediated anti-apoptotic pathway. *Oncogene*, in press.
- Hu, C. M.; Zhu, J.; Guo, X. E.; Chen, W.; Qiu, X. L.; Ngo, B.; Chien, R.; Wang, Y. V.; Tsai, C. Y.; Wu, G. K.; Kim, Y.; Lopez, R.; Chamberlin, A. R.; Lee, E. Y. H. P.; Lee, W. H., Novel small molecules disrupting Hec1/Nek2 interaction ablate tumor progression by triggering Nek2 degradation through a death-trap mechanism. *Oncogene*, in press.

Research Interests

This lab co-discovered the first human tumor suppressor gene, Retinoblastoma gene (RB), in late 1980 that plays essential roles in maintaining genomic stability and preventing tumor formation. In addition, we have elucidated RB interaction networks, which modulate RB suppressing activity. One of the RB-interacting proteins, Hec1, is overly expressed in most cancer cells and plays essential roles in chromosome segregation by interacting with several proteins that modulate the G2/M phase. Hec1 is phosphorylated by a mitotic kinase Nek2. We have identified small molecules that disrupt the interaction between Nek2 and Hec1, and may offer a novel agent to treat cancer. We worked on two human breast cancer susceptibility genes, BRCA1 & BRCA2 and have established their dual participation in transcription regulation and DNA damage repair. The BRCA2 via its BRC repeats binds to RAD51, which important for recombination reaction of DNA. Small molecules that disrupt the interaction between BRC repeat and Rad51 have been isolated. These small compounds offer a potential to develop new combinatorial treatment with chemotherapy or radiation therapy. Recently, we are focus in elucidation of the roles of microenvironment in breast and pancreatic tumorigenesis. Our previous work has identified a novel Interleukin-17B receptor / Interleukin-17B (IL-17RB/IL-17B) pathway can promote tumorigenic activity in IL-17RB overexpression breast and pancreatic cancer cells. Treatment with antibody against IL-17RB blocked tumor metastasis and promoted survival in a mouse xenograft model. These findings illustrate a key mechanism underlying the highly aggressive characteristics of these cancers and provide a practical approach to tackle these diseases.

本研究室在過去發現並研究第一個人類抑癌基因，RB 基因。經由了解其相互作用蛋白質，我們發現 Hec1 對癌細胞的重要性，並找到一個小分子可以抑制 Hec1 的功能而達到抑癌的效果。在研究乳癌相關基因方面，我們著重於探討 BRCA1 和 BRCA2 在 DNA 修復上的重要性，同時也找到一個小分子，可藉由阻礙 BRCA2/Rad51 複合體的形成而達到抑癌作用。最近，我們更探討癌細胞與微環境之間的相互作用、機制。我們證明 IL17RB/IL17B 訊息傳導途徑在癌症中的重要性，可做為治療的新標的；更重要的是我們利用老鼠模式，針對 IL17RB/IL17B 過度表達的癌症做 IL17RB 抗體治療，抗癌效果非常顯著。



Microenvironment and tumorigenesis --- Elucidation of the interplay between breast / pancreatic cancer cells and its microenvironment

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Education and Positions

- Ph.D., Molecular Microbiology and Immunology, The Johns Hopkins University, 1998
- Postdoctoral Fellow, Columbia University, 1998-2003
- Associate Research Scientist, Columbia University, 2003-2004
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, 2004-2009
- Associate Research Fellow, Genomics Research Center, Academia Sinica, 2009-2014
- Research Fellow, Genomics Research Center, Academia Sinica, 2014-present
- Adjunct Associate Professor, Institute of Immunology, National Taiwan University, 2010

Honor

- Betty Lee Hampil Honorary Fellowship, Dept. of Molecular Microbiology and Immunology, The Johns Hopkins University, 1995
- Phi Beta Kappa, The Johns Hopkins University, 1999
- The Leukemia and Lymphoma Society Fellowship, 1999-2002
- Li Foundation Heritage Prize, 2005
- 1st ASAIHL-Scopus Young Scientist Award, 2008
- Career Development Award, Academia Sinica, 2010
- Outstanding Research Award, National Science Council, 2013
- Young Scientist Award, TienTe Lee Biomedical Foundation, 2014

Selected Publications

- Shaffer, A. L.; Lin, K.-I.; Kuo, T.-C.; Yu, X.; Hurt, E. M.; Rosenwald, A.; Giltnane, J. M.; Yang, L.; Zhao, H.; Calame, K.; Staudt, L. M., Blimp-1 orchestrates plasma cell differentiation by extinguishing the mature B cell gene expression program. *Immunity*, 2002, *17*, 51-62.
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- Ying, H.-Y.; Su, S.-T.; Hsu, P.-H.; Chang, C.-C.; Lin, I.-Y.; Tseng, Y.-H.; Tsai, M.-D.; Shih, H.-M.; Lin, K.-I., SUMOylation of Blimp-1 is critical for plasma cell differentiation. *EMBO Rep*, 2012, *13*, 631-7.
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- Chiang, M.-F.; Yang, S.-Y.; Lin, I-Y.; Hong, J.-B.; Lin, S.-J.; Ying, H.-Y.; Chen, C.-M.; Wu, S.-Y.; Liu, F.-T.; Lin, K.-I., Inducible deletion of the Blimp-1 gene in adult epidermis causes granulocyte-dominated chronic skin inflammation in mice. *Proc Natl Acad Sci USA*, 2013, *110*, 6476-81.
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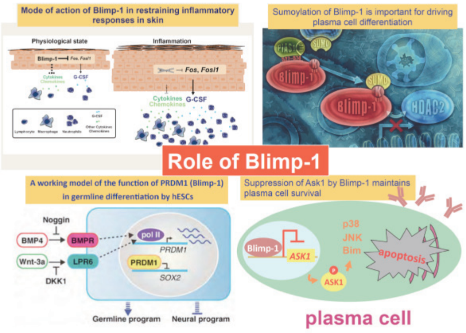
- Chen, J.-R.; Yu, Y.-H.; Tseng, Y.-C.; Chiang, W.-L.; Chiang, M.-F.; Ko, Y.-A.; Chiu, Y.-K.; Ma, S.-H.; Wu, C.-Y.; Jan, J.-T.; Lin, K.-I.; Ma, C.; Wong, C.-H., Vaccination of monoglycosylated hemagglutinin induces cross-strain protection against influenza virus infections. *Proc Natl Acad Sci USA*, 2014, *111*, 2476-81.

Research Interests

Regulatory mechanisms in immune system

Research work in Lin's laboratory combines molecular biology and mouse gene knockout model to understand the mechanisms of gene expression or post-translational modification in regulation of the immune system development and function. The major research interests are listed in the follows:

- Gene regulatory circuits in the immune system, focusing on studying the mode of action of a master regulator of cellular differentiation, Blimp-1
- Molecular mechanisms of tumorigenesis of plasma cells and mature B cells
- Transcriptional regulation in dendritic cell development and maturation
- Glycomics and glycobiology in B cells



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Education and Positions

- D.V.M., National Taiwan University, 1983
- Ph.D., Pathology, University of Southern California, 1991
- Postdoctoral Fellow, University of California at San Diego, 1991-1993
- Postgraduate Biochemist, University of California at San Diego, 1993-1994
- Senior Research Associate, Stanford University, 1994-1998
- Associate Investigator of Medical Education and Research, Kaohsiung Veterans General Hospital, 1998-2005
- Adjunct Associate Professor of Veterinary Medicine, National Taiwan University, 1998-present
- Associate Research Fellow, Genomics Research Center, Academia Sinica, 2005-present
- Adjunct Associate Professor of Biology, National Defense Medical College, 2006-present

Honors

- National Cancer Institute Post-Doctoral Fellowship, 1991-1993
- First Prize, Tumor Section, Congress for the Neurological Surgeons, 1997
- Young Investigator Award, American Association for the Neurological Surgeons and Congress for Neurological Surgeons, 1998
- First prize, Taiwan Association for Veterinary Medicine, 1999
- Second Prize, Asia-Pacific Congress on Oral cavity Cancer, 2008
- Editorial Board, Am J Cancer Res, 2011, Journal of Cancer Therapeutics and Research, 2011
- ad hoc reviewer for Ann Surg Oncol., BBA-Mol Cell Res, Biochimie, Brit J Cancer, Cancer, Cancer Gene Therapy, Cancer Lett, Cancer Res, Clin Exp Metastasis, Eur J Cancer, Gene Ther, Gut, Histol Histopathol, Int J Cancer, J Biomed Biotech, J Cancer Mol, J Phys Chem C, Nanoscale, Oncogene, Oral Oncol, PLoS One, Stem Cells

Selected Publications

- Tsai, W. C.; Hsu, P. W.; Lai, T. C.; Chau, G. Y.; Lin, C. W.; Chen, C. M.; Lin, C. D.; Liao, Y. L.; Wang, J. L.; Chau, Y. P.; Hsu, M. T.; Hsiao, M.; Huang, H. D.; Tsou, A. P., MicroRNA-122, a tumor suppressor microRNA that regulates intrahepatic metastasis of hepatocellular carcinoma. *Hepatology*, 2009, *49*, 1571-82.
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- Hua, K. T.; Tan, C. T.; Johansson, G.; Lee, J. M.; Yang, P. W.; Lu, H. Y.; Chen, C. K.; Su, J. L.; Chen, P. B.; Wu, Y. L.; Chi, C. C.; Kao, H. J.; Shih, H. J.; Chen, M. W.; Chien, M. H.; Chen, P. S.; Lee, W. J.; Cheng, T. Y.; Rosenberger, G.; Chai, C. Y.; Yang, C. J.; Huang, M. S.; Lai, T. C.; Chou, T. Y.; Hsiao, M.; Kuo, M. L., N-α-acetyltransferase 10 protein suppresses cancer cell metastasis by binding PIX proteins and inhibiting Cdc42/Rac1 activity. *Cancer Cell*, 2011, *19*, 218-31.
- Jan, Y. H.; Tsai, H. Y.; Yang, C. J.; Huang, M. S.; Yang, Y. F.; Lai, T. C.; Lee, C. H.; Jeng, Y. M.; Huang, C. Y.; Su, J. L.; Chuang, Y. J.; Hsiao, M., Adenylate kinase-4 is a marker of poor clinical outcomes that promotes metastasis of lung cancer by downregulating the transcription factor ATF3. *Cancer Res*, 2012, *72*, 5119-29.
- Lin, F. C.; Liu, Y. P.; Lai, C. H.; Shan, Y. S.; Cheng, H. C.; Hsu, P. I.; Lee, C. H.; Lee, Y. C.; Wang, H. Y.; Wang, C. H.; Cheng, J. Q.; Hsiao, M.; Lu, P. J., RUNX3-mediated transcriptional inhibition of Akt suppresses tumorigenesis of human gastric cancer cells. *Oncogene*, 2012, *31*, 4302-16.
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- Liu, Y. P.; Liao, W. C.; Ger, L. P.; Chen, J. C.; Hsu, T. I.; Lee, Y. C.; Chang, H. T.; Chen, Y. C.; Jan, Y. H.; Lee, K. H.; Zeng, Y. H.; Hsiao, M.; Lu, P. J., Carboxyl-terminal modulator protein positively regulates akt phosphorylation and acts as an oncogenic driver in breast cancer. *Cancer Res*, 2013, *73*, 6194-205.
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Research Interests

- Targeting tumor growth/survival pathways to enhance tumor chemosensitivity and/or radiosensitivity.
- Novel strategies to overcome tumor metastasis
  - Novel microarray based gene discovery associated with tumor metastasis
  - Viral or pharmacological compounds based inhibition of PI3K/Akt pathway to inhibit tumor invasion and migration
  - Therapeutical interventions using tumor metastasis suppressor genes in preclinical trial settings
  - Establishment of novel real-time 3D quantifiable metastatic tumor models to investigate tumor metastasis dynamics and evaluate therapeutical efficacy
  - Utilization of high-throughput proteomic analysis for the identification of novel tumor metastasis markers and therapeutical evaluations.
- Development of nanoparticle-mediated high-throughput transfection platforms to identify and characterize novel gene expression functional consequences.

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Education and Positions

- Ph.D., Developmental Biology Program, University of Bath, 2002
- Postdoctoral Fellow, Centre For Regenerative Medicine, University of Bath, 2002-2004
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, 2004-2012
- Associate Research Fellow, Genomics Research Center, Academia Sinica, 2012-present
- Deputy Director, Genomics Research Center, Academia Sinica, 2013-present

Honors

- Travel award of Japan Society for the promotion of science for attending NPG Nature Asia-Pacific Network Meeting, 2007
- Travel award of International Society of Stem Cell Research for attending 10th ISSCR Annual Meeting, 2012

Selected Publications

- Shen, C. N.; Slack, J. M.; Tosh, D., Molecular basis of transdifferentiation of pancreas to liver. *Nat Cell Biol*, 2000, *2*, 879-87.
- Shen, C. N.; Seckl, J. R.; Slack, J. M.; Tosh, D., Glucocorticoids suppress beta-cell development and induce hepatic metaplasia in embryonic pancreas. *Biochem J*, 2003, *375*, 41-50.
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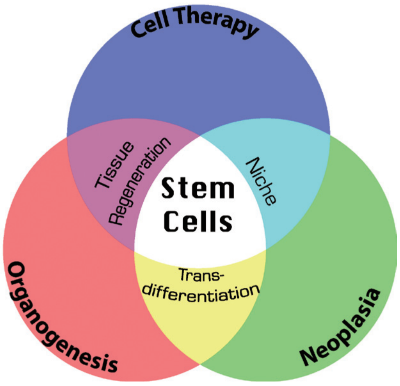
- Tsai, H. A.; Wu, R. R.; Lee, I. C.; Chang, H. Y.; Shen, C. N.; Chang, Y. C., Selection, enrichment, and maintenance of self-renewal liver stem/progenitor cells utilizing polypeptide polyelectrolyte multilayer films. *Biomacromolecules*, 2010, *11*, 994-1001.
- Tsai, S. T.; Tsou, C. C.; Mao, W. Y.; Chang, W. C.; Han, H. Y.; Hsu, W. L.; Li, C. L.; Shen, C. N.; Chen, C. H., Label-free quantitative proteomics of CD133-positive liver cancer stem cells. *Proteome Sci*, 2012, *10*, 69.
- Lin, Y. H.; Chang, H. M.; Chang, F. P.; Shen, C. R.; Liu, C. L.; Mao, W. Y.; Lin, C. C.; Lee, H. S.; Shen, C. N., Protoporphyrin IX accumulation disrupts mitochondrial dynamics and function in ABCG2-deficient hepatocytes. *FEBS letters*, 2013, *587*, 3202-9.

Research Interests

Somatic Cell Reprogramming and Pancreatic Diseases

The explosion of interest in somatic cell reprogramming has been fueled by their potential as a limitless source of cells to repair damaged tissues. However, whether naturally occurring cell reprogramming such as transdifferentiation (metaplasia) has a role in disease progression will also be needed to address. Currently, we have three research directions: (1) Islet transplantation has been recognized as an efficient therapeutic approach for treating type I diabetes, however, “shortage of donor supply” limited the usage. Whether stem cells exist in adult pancreatic tissues remains unclear, we have been trying to covert (transdifferentiate) cells of alternative resources to beta-cells. (2) Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal forms of pancreatic cancer as the overall five years survival rate was 6%. It has been shown that the exocrine pancreas undergoes acinar-to-ductal transdifferentiation (metaplasia) in both chronic pancreatitis and pancreatic cancer suggesting a key role of acinar cell metaplasia in pancreatic carcinogenesis. We have been trying to identify the key factor that modulating acinar cell reprogramming in pancreatitis which would contribute to development of cancer in pancreas. (3) Existences of cancer stem/initiating cells in PDAC and other forms of solid tumors may be the causes of chemo-resistance and cancer metastasis in patients. We are working on defining whether cancer stemness is derived from reprogramming and developing strategies for targeting cancer stem/initiating cells.

體細胞重新編程的研究，可以提供線索幫助我們鑑定細胞分化的關鍵機制，明瞭在促成組織修復及再生的機轉及搜尋癌症轉化的早期起始基因。我們目前有三個研究方向：(1) 由於糖尿病的高盛行率及胰島移植的來源絕對缺乏，我們利用重新編程將組織細胞轉變功能胰島細胞及糖尿病小鼠模式，以驗證及開發進行糖尿病自體移植治療方法。(2) 在胰臟癌化的過程中發現有胰腺細胞重新編程轉分化) 產生肝細胞或胰管細胞的現象，本實驗室結合細胞重新編程或建構胰腺專一表達突變基因的標定鼠及原位胰臟癌小鼠的方式，進行胰臟癌化的機制研究。(3) 由於胰臟腫瘤幹細胞是造成胰腺癌高轉移性及抗藥性的重要原因，我們嘗試探討胰臟腫瘤幹細胞的特性是否來自癌化過程的特定細胞的重新編程，並以此為標的開發新的治療策略。



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Education and Positions

- Ph.D., Graduate Institute of Epidemiology, School of Public Health, National Taiwan University, Taipei, Taiwan, 2006
- Postdoctoral Fellow, Genomics Research Center, Academia Sinica, Taipei, Taiwan, 2006-2011
- Associate Research Fellow, Molecular and Genomic Epidemiology Center, China Medical University Hospital, Taichung, Taiwan, 2011-2013
- Associate Professor, Graduate Institute of Clinical Medicine, China Medical University, Taichung, Taiwan, 2011-2013
- Associate Research Fellow, Genomics Research Center, Academia Sinica, Taipei, Taiwan, 2013-present

Honors

- Prof. K-P Chen Award for the Best Public Health Paper, Taiwan Public Health Association, 2004
- Distinguished Postdoctoral Scholar of Academia Sinica, 2007-2008
- The 20th Wang Ming-Ning Award , 2010 (as a REVEAL-HBV study group member)
- Ta-You Wu Memorial Award, National Science Council, Taiwan, 2013
- The 2013 Award for Outstanding Contributions in Science and Technology, Executive Yuan, 2013 (co-awardee: Prof. Chien-Jen Chen and Dr. Mei-Hsuan Lee)

Selected Publications

- Yang, H. I.; Lu, S. N.; Liaw, Y. F.; You, S. L.; Sun, C. A.; Wang, U. Y.; Hsiao, C. K.; Chen, P. J.; Chen, D. S.; Chen, C. J., Taiwan Community-Based Cancer Screening Project Group. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med,* 2002, *347*, 168-74.
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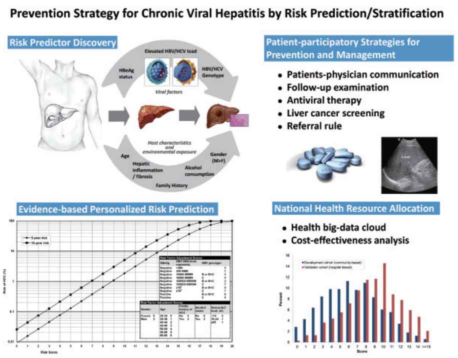
- Liu, J.; Yang, H. I.; Lee, M. H.; Lu, S. N.; Jen, C. L.; Wang, L. Y.; You, S. L.; Iloeje, U. H.; Chen, C. J., Incidence and determinants of spontaneous hepatitis B surface antigen seroclearance: a community-based follow-up study. *Gastroenterology*, 2010, *139*, 474-82.
- Yang, H. I.; Yuen, M. F.; Chan, H. L. Y.; Han, K. H.; Chen, P. J.; Kim, D. Y.; Ahn, S. H.; Chen, C. J.; Wong, V. W. S.; Seto, W. K., REACH-B Working Group. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol*, 2011, *12*, 568-74.
- Yang, H. I.; Hung, H. L.; Lee, M. H.; Liu, J. C.; Jen, C. L.; Su, J.; Wang, L. Y.; Lu, S. N.; You, S. L.; Iloeje, U. H.; Chen, C. J., Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer–HBV (REVEAL-HBV) Study Group. Incidence and determinants of spontaneous seroclearance of hepatitis B e antigen and DNA in patients with chronic hepatitis B. *Clin Gastroenterol Hepatol*, 2012, *10*, 527-34.

Research Interests

Our lab is dedicating to the following topics:

- **Hepatitis Epidemiology:** Delineating incidence and determinants of milestone transitions and disease progression in the natural history of chronic hepatitis B and C using longitudinal follow-up study
- **Translational Epidemiology:** Development and validation of risk prediction instruments which integrated multiple non-invasive clinical parameters for the prediction of marker transition and adverse sequelae of chronic hepatitis B and C
- **Immunoepidemiology of Viral Hepatitis:** Investigating roles of immunological factors of host on important outcomes of viral hepatitis using high-throughput molecular and genomic techniques
- **Immunoprevention of Major Cancers:** Exploring useful genomic, proteomic, and glycomic pre-diagnostic biosignatures for predicting major cancers in order to develop novel tactics in cancer early diagnosis and cancer preventive vaccines

我們利用一個長期追蹤世代及流行病學研究方法，闡明慢性 B 型及 C 型肝炎自然史中重要血清標記轉換及疾病進展的發生率和多重風險決定因子。其次，我們結合已發現的非侵入性臨床決定因子，建構並驗證可用以預測慢性 B 型及 C 型肝炎病患血清標記轉換及發生末期肝疾的風險預測模式。我們目前的研究著重於利用高通量技術如全基因體研究、次世代定序、多重蛋白質檢測、以及醣晶片來探討宿主（免疫）因子在慢性病毒性肝炎、肝硬化及肝細胞癌所扮演的角色。我們的另一目標是利用發病前生物檢體，探索主要癌症發生前之基因體、蛋白質體、以及醣體生物標幟，進而研發出新的癌症預防策略如癌症預防疫苗並改善癌症早期診斷工具。



Wu-Shiun Hou 侯武勳

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Education and Positions

- Ph.D., Biomedical Sciences, Mount Sinai School of Medicine, New York University, 2001
- Postdoctoral Associate, Massachusetts Institute of Technology, 2001-2006
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, 2006-present

Honors

- Arthritis Foundation Travel Awards, 2001 and 2003

Selected Publications

- Hou, W. S.; Bromme, D.; Zhao, Y.; Mehler, E.; Dushey, C.; Weinstein, H.; Miranda, C. S.; Fraga, C.; Greig, F.; Carey, J.; Rimoin, D. L.; Desnick, R. J.; Gelb, B. D., Characterization of novel cathepsin K mutations in the pro and mature polypeptide regions causing pycnodysostosis. *J Clin Invest*, 1999, *103*, 731-8.
- Li, Z.; Hou, W. S.; Bromme, D., Collagenolytic activity of cathepsin K is specifically modulated by cartilage-resident chondroitin sulfates. *Biochemistry*, 2000, *39*, 529-36.
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- Hou, W. S.; Li, Z.; Buttner, F. H.; Bartnik, E.; Bromme, D., Cleavage site specificity of cathepsin K toward cartilage proteoglycans and protease complex formation. *Biol Chem*, 2003, *384*, 891-7.
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Research Interests

The research in the Hou lab is focusing on the mechanisms underlying dendritic cell homeostasis. Using genetics, biochemical and immunologic approaches, the lab are specifically studying on:

- Control of dendritic cell survival and turnover
- Interaction of dendritic cell turnover with infection agents and tumors
- Deregulation of dendritic cell survival/turnover in immune system and disease development

本實驗室專注於研究免疫樹突細胞的生命週期及其數量恆定的調控。利用基因、生化、及免疫學的方法，我們正對以下主題進行研究：

- 免疫樹突細胞的生存及更新的調控
- 免疫樹突細胞更新的調控與感染媒介及腫瘤的互動與影響
- 免疫樹突細胞的生存及更新的調控失衡對免疫系統及疾病之影響與發展

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Education and Positions

- B.S. Department of Medical Technology, National Taiwan University, Taiwan, 1988-1992
- M.S. Institute of Molecular Medicine, National Taiwan University, Taiwan, 1992-1994
- Ph.D. Institute of Microbiology, National Taiwan University, Taiwan, 1995-2000
- Postdoctoral Fellow, Graduate Institute of Microbiology, College of Medicine, National Taiwan University, Taiwan, 2001-2003
- Postdoctoral Fellow/Associate, Molecular, Department of Cellular, and Developmental Biology, Yale University, USA, 2003-2007
- Assistant Research Fellow, Stem Cell Program, Genomics Research Center, Academia Sinica, Taiwan, 2007-present
- Co-PI, National RNAicore Facility Plateform, Academia Sinica, 2009-present
- Adjunct Assistant Professor, Genomics and System Biology Program, College of Life Science, National Taiwan University, Taiwan, 2010-present

Honors

- Outstanding Paper Award, National Taiwan University, 2002
- Ruth L. Kirschstein National Research Service Award Fellowship,2003-2005

Selected Publications

- Lu, J., Chen, S.Y., Chua, H.H., Liu, Y.S., Huang, Y.T., Chang, Y., Chen, J.Y., Sheen, T.S., and Tsai, C.H., Upregulation of tyrosine kinase TKT by the Epstein-Barr virus transactivator Zta. *J Virol*, 2000, *74*, 7391-9.
- Lu, J., Chua, H.H., Chen, S.Y., Chen, J.Y., and Tsai, C.H., Regulation of matrix metalloproteinase-1 by Epstein-Barr virus proteins. *Cancer Res*, 2003, *63*, 256-62.
- Lu, J., Lin, W.H., Chen, S.Y., Longnecker, R., Tsai SC., Chen C.L., and Tsai, C.H., Syk tyrosine kinase mediates Epstein-Barr virus latent membrane protein 2A-induced cell migration in epithelial cells. *J Biol Chem*, 2006, *281*, 8806-14.
- Lu, J., Hou, R., Booth, C.J., Yang, S.H., Snyder, M., Defined culture conditions of human embryonic stem cells. *PNAS*, 2006, *103*, 5688-93.
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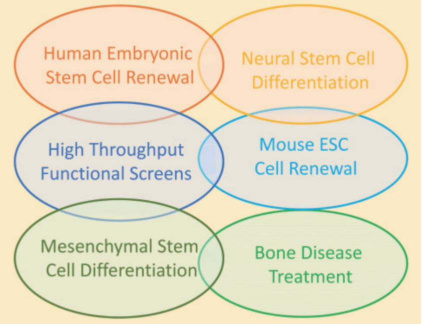
- Lu, F.L., Yu, C.C., Chiu, H.H., Liu, H.E., Chen, S.Y., Lin, S.F., Goh, T.Y., Hsu, H.C., Chien, C.H., Wu, H.C., Chen, M.S., Schuyler, S.C., Hsieh, W.S., Wu, M.H., Lu, J.,* Sonic hedgehog antagonists induce cell death in acute myeloid leukemia cells in the presence of lipopolysaccharides, tumor necrosis factor-α, or interferons. *Invest New Drug*, 2013, *31*, 823-32.
- Wang, C.H., Ma, N., Lin, Y.T., Wu, C.C., Wu, H.J., Yu, C.C., Hsiao, M., Lu, F.L., Schuyler, S.C., and Lu, J.,* Array-based high throughput screen in mouse embryonic stem cells with shRNAs. *Curr Protoc Stem Cell Biol*, 2013, *26*, 5C.3.1-5C.3.19.
- Huang H.N., Chen, S.Y., Hwang, S.M., Yu, C.C., Su, M.W., Mai, W., Wang, H.W., Cheng,W.C., Schuyler, S.C., Ma, N., Lu, F.L., and Lu, J.,* miR-200c and GATA binding protein 4 regulate human embryonic stem cell renewal and differentiation. *Stem Cell Res*, 2013, *12*, 338-53.
- Liu, Y.C., Kao, Y.T., Huang, W.K., Lin, K.Y., Wu, S.C., Schuyler, S.C., Li, L.Y., Leigh L.F., Lu, J.,* CCL5/RANTES is important for inducing osteogenesis of human mesenchymal stem cells. *BioSci Trends*, 2014, *8*, 138-43.

Research Interests

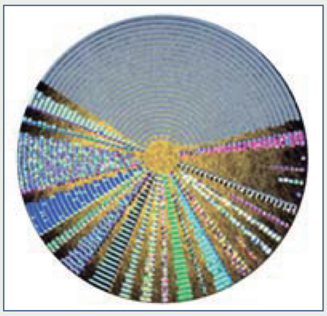
High throughput functional screens pinpoints key factors for cell fate determination

To efficiently pinpoint factors critical for cell fate determination, high throughput systematically functional screens were performed in mouse/human embryonic stem cells (ESCs), and mesenchymal stem cells (MSCs). We established the first shRNA screen in ESCs. With a shRNA library of kinases and phosphatases contains 4796 shRNAs, we identified 244 genes essential for mouse ESC renewal. Among them, Nme6 and Nme7 are essential for 8 stemness genes expressions. With 517 shRNAs target genes are differentially expressed in undifferentiated human ESCs, we performed a shRNA functional screen and found 86 genes essential for human ESC renewal. To fulfill the unmet need of bone diseases, a gain-of-function screen was performed with an overexpression library contains 12380 genes. 9 candidate genes are found to be essential and sufficient to promote the osteogenesis of human MSCs. By this method, we found soluble factor that can completely treat and prevent osteoporosis.

為了有效地找尋決定細胞的命運的樞紐因子，我們在小鼠 / 人類胚胎幹細胞，和間質幹細胞進行高通量系統性功能篩選。我們建立了第一個在胚胎幹細胞的 shRNA 篩選。我們以 4796 個 shRNA 進行激酶和磷酸酶的功能性篩選，並發現了 244 個基因對老鼠胚胎幹細胞的自我更新是必要的。其中，Nme6 和 Nme7 對 8 個幹細胞特性基因的表達是必需的。我們另以在未分化的胚胎幹細胞和分化細胞差異表現基因所設計的 517 個 shRNA，在人類胚胎幹細胞進行功能性篩選，發現 86 個基因對人類胚胎幹細胞的自我更新是必要的。為了解決骨骼疾病中待解決的問題，我們在間質幹細胞過度表達 12380 個基因。目前發現至少有 9 個候選基因對成骨作用是必要。藉由這個方法，我們發現可溶性因子可以完全地治療與預防骨質疏鬆症。



Physical and Computational Genomics Division



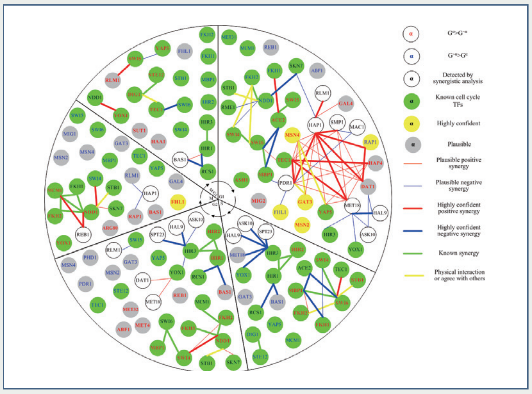
This Division has two major goals. One is technology and instrumentation development and the other is computational bioinformatic technology development. For physical genomics program, it aims to develop new tools with improved sensitivity and resolution for use in studying the dynamics of complex biological systems. Current interests include development of biological mass spectrometry, microarray and nanotechnology for genomic and proteomic research, biomarker discovery, biophotomics for single cell research, fabrication of biological and biomimetic materials, development of functional supramolecular structures for disease diagnosis, novel detection technologies for circulating tumor cells (CTC) . For computational genomics, the aim is to pursue functional and evolutionary genomics as well as structural informatics, using a combination of tools and resources from bioinformatics, computer sciences, statistics, molecular biology, biochemistry, genetics and evolution. It focuses on development of methods for analysis of genomic sequences, prediction of alternative splicing especially on trans-alternative splicing, identification of gene regulation pathways, study of protein interaction networks, study of regulatory networks, structure-based molecular modeling and design, and prediction of pharmacology. The long-term goal is to develop computational models for use in understanding cellular functions and other biomedical applications such as in silico drug prediction.

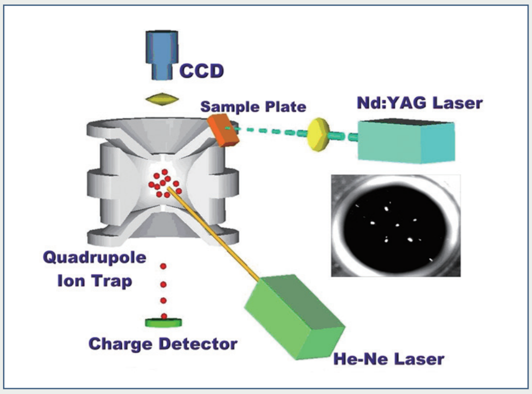
In the future, we will continue to focus our effort in the above areas. We believe there will be a good possibility that we will be in a leading position worldwide in mass spectrometry development and biomarker discovery, comparative genomics of human and apes, and platform and technology build up for single cell transcriptomics and proteomics.

物理與資訊基因體學專題中心

本研究組有兩個主要的研究方向，一為創新儀器與技術發展研究，另一為資訊基因體學研究。在創新儀器與技術發展部份，主要目標為發展高靈敏度與高解析度的儀器與檢測平台，針對複雜的生物樣品做分析。此部份研究包含發展生物質譜儀、發展微陣列檢測系統、新柰米生醫技術、找尋疾病生物標的物、製造生物性與仿生性材料、發展可應用於疾病診斷的功能性超分子結構、測量血液中循環性癌細胞。在資訊基因體學研究部份，主要目標為結合生物資訊計算平台、統計學、電腦科學、生物化學、分子生物學與演化學等資料，發展功能與演化基因體研究平台。此部分研究著重於發展準確的分析方法運用於分析基因序列、預測基因的多樣性切割、分析基因調控路徑、研究蛋白質交互作用調控網絡、結構分子模擬系統。長程目標在於發展可應用於研究細胞功能與其他生物醫學相關研究的電腦模擬。

在未來，我們將會著重於上述研究重點。我們將更積極地致力於研發新式質譜儀、疾病生物標的物分析平台、跨物種分析、比較人類和大猿間的基因體和蛋白質體的研究、蛋白體學與轉錄體學研究。我們相信上述的研發成果將使我們在全球在上述的某些領域具有領導的地位。





Chung-Hsuan Chen 陳仲瑄

Distinguished Research Fellow
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特聘研究員兼中心主任
物理與資訊基因體學專題中心執行長
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Education and Positions

- Ph.D., Chemistry, University of Chicago, 1974
- Postdoctoral Fellow, Oak Ridge National Laboratory, 1974-1976
- Research Scientist, Oak Ridge National Laboratory, 1976-1989
- Senior Scientist and Project Leader, Oak Ridge National Laboratory, 1989-2005
- Adjunct Professor, Department of Physics and Astronomy, Vanderbilt University, 1990-2005
- Adjunct Professor, Department of Physics, University of Tennessee, Knoxville, 1993-2005
- Research Fellow and Key Technology Division Head, Genomics Research Center; Academia Sinica, 2005-2006
- Distinguished Research Fellow and Acting Director, Genomics Research Center; Academia Sinica, 2006-2007
- Director, Genomics Research Center, Academia Sinica, 2007-present

Honors

- R&D-100 Awards (top 100 Inventions of the year):
  Rare Gas Atom Counter, 1984
  Crystal Laser Beam Monitor, 1987
  Non-CFC Freon Leak Detector, 1992
- Editorial Board: Rapid Communication in Mass Spectrometry
- American Physical Society Fellow, 1995
- Advancement of Outstanding Scholarship Award, 2004-2009
- Fellow, American Association for the Advancement of Science (AAAS), USA, 2009
- Academician, Academia Sinica, 2010

Selected Publications

- Peng, W. P.; Lin, H. C.; Lin, H. H.; Chu, M.; Yu, A. L.; Chang H. C.; Chen, C. H., Charge-monitoring laser-induced acoustic desorption mass spectrometry for cell and microparticle mass distribution measurement. *Angew Chem Int Ed*, 2007, *46*, 3865-9.
- Peng, W. P.; Lin, H. C.; Chu, M. L.; Chang, H. C.; Lin, H. H.; Yu, A. L.; Chen, C. H., Charge monitoring cell mass spectrometry. *Anal Chem*, 2008, *80*, 2524-30.
- Hsu, N. Y.; Tseng, S. Y.; Wu, C. Y.; Wong, C. H.; Chen, C. H., Desorption ionization of biomolecules on metals. *Anal Chem*, 2008, *80*, 5203-10.
- Hsiao, C. R.; Chen, C. H., Characterization of DNA chips by nanogold staining. *Anal Chem*, 2009, *389*, 118-23.
- Chang, W. C.; Huang, M. S.; Yang, C. J.; Lai, T. C.; Hsiao, M.; Chen, C. H., Dermicidin identification from exhaled air for lung cancer diagnosis. *Eur Respir J*, 2010, *35*, 1182-5.
- Lin, H. C.; Lin, H. H.; Kao, C. Y.; Yu, A. L.; Peng, W. P.; Chen, C. H., Quantitative measurement of nano/micro particle endocytosis with cell mass spectrometry. *Angew Chem Int Ed*, 2010, *49*, 3460-64.
- Sudhir, P. R.; Chen, C. H.; Pavana Kumari, M.; Wang, M. J.; Tsou, C. C.; Sung, T. Y.; Chen, J. Y.; Chen, C. H., Label-free quantitative proteomics and N-glycoproteomics analysis of KRAS-activated human bronchial epithelial cells. *Mol Cell Proteomics*, 2012, *11*, 901-15.
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- Hsu, Y. F.; Lin, J. L.; Chu, M. L.; Wang, Y. S.; Lee, Y. T.; Chen, C. H., Macromolecular ion accelerator. *Anal Chem*, 2012, *84*, 5765-9.
- Gillig, K. J.; Chen, C. H., A critical examination of gas-phase protein conformation/multimer ion formations by electrospray ion mobility-mass spectrometry. *Anal Chem*, 2013, *85*, 2177-82.
- Hsu, Y. F.; Lin, J. L.; Chu, M. L.; Wang, Y. S.; Chen, C. H., Macromolecular Ion Accelerator Mass Spectrometer. *Analyst*, 2013, *138*, 7384-91.
- Özdemir, Abdil; Lin, J. L.; Gillig, K. J.; Chen, C. H., Kelvin Dropper Spray Ionization. *Analyst*, 2013, *138*, 6913-23.
- Sudhir, P. R.; Kumari, M.; Hsu, W. T.; Massiot, J.; Chen, C. H.; Kuo, H. C.; Chen, C. H., Quantitative Proteomics of Protein Complexes and Their Implications for Cell Reprograming and Pluripotency. *Journal of Proteome Research* 2013, *12*, 5878-90.

Research Interests

Chemical Physics and its application in technology development

Research work in Chen laboratory covers a broad spectrum of atomic, molecular and solid state physics as well as their applications in ultra-sensitive detection technology development. The major research interests are listed in the follows:

- Genomic and Proteomic Technology
- Biomolecular Mass Spectrometry
- Microarray hybridization detection
- DNA typing for forensic applications
- Instrumentation Development for Ultra-low Level Pollutants Detection
- Nanoscience for biomedical applications
- High Temperature Superconductors
- Atomic and Molecular Spectroscopy
- Crossed Molecular Beam for Reaction Dynamics Studies
- Kinetics of F-centers and Self-trapped Excitons in Alkali Halide Crystals

陳仲瑄博士實驗室主要研究方向如下：

- 基因體和蛋白體科技
- 生物分子質譜
- 微米排列雜交測量
- 核酸測定在犯罪學的應用
- 超微量污染物測量
- 奈米生物醫學
- 高溫超導體
- 原子和分子光譜
- 分子束和化學動力學

Ying-Chih Chang 張瑛芝

Research Fellow

基因體研究中心研究員

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Education and Positions

- Ph.D., Chemical Engineering, Stanford University, 1998
- Senior Engineer, MMC (now Seagate), 1998
- Postdoctoral Fellow, Stanford University/ Affymetrix, 1998-1999
- Assistant Professor, Department of Chemical Engineering and Materials Science, and Biomedical Engineering, University of California, Irvine, 1999-2003
- Associate Research Fellow to Research Fellow, Genomics Research Center, Academia Sinica, 2004-present
- Joint Appointment: Consulting Professor of Chemical Engineering in the School of Engineering, Stanford University, 2014-present

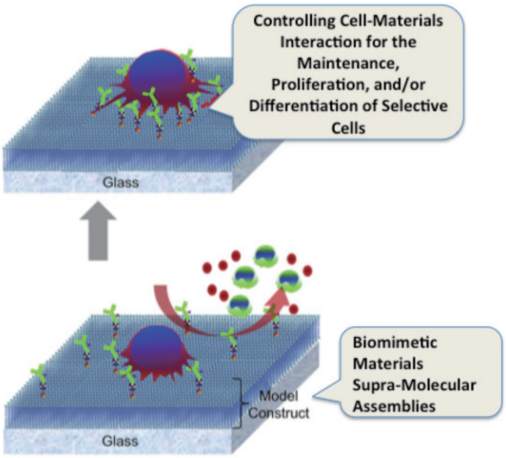
Selected Publications

- Wang, Y.; Chang, Y.-C., Grafting of homo- block co-polypeptides on solid substrates by an improved surface-initiated vapor deposition polymerization. *Langmuir*, 2002, *18*, 9859-66.
- Wang, Y.; Chang, Y.-C., Preparation of unidirectional end-grafted alpha-helical polypeptides by solvent quenching. *J Am Chem Soc*, 2003, *125*, 6376-7.
- Wang, Y.; Chang, Y.-C., Synthesis and conformational transition of surface tethered polypeptide: poly(L-glutamic acid). *Macromolecules*, 2003, *36*, 6503-10.
- Yang, C.-T.; Wang, Y. L.; Yu S.; Chang, Y.-C., Controlled molecular organization of surface macromolecular assemblies based on stimuli-responsive polypeptide brushes. *Biomacromolecules*, 2008, *10*, 58-65.
- Huang, C.-J.; Cho, N.-J.; Hsu, C.-J.; Frank, C. W.; Chang, Y.-C., Type I collagen-functionalized supported lipid bilayer as a cell culture platform. *Biomacromolecules*, 2010, *11*, 1231-40.
- Huang, C.-J.; Tseng, P.-Y.; Chang, Y.-C., Effects of extracellular matrix protein functionalized fluid membrane on cell adhesion and matrix remodeling. *Biomaterials*, 2010, *31*, 7183-95.
- Huang, C.-J.; Chien, Y.-L.; Ling, T.-Y.; Cho, H.-C.; Yu, J.; Chang, Y.-C., The influence of collagen film nanostructure on pulmonary stem cells and collagen-stromal cell interactions. *Biomaterials*, 2010, *31*, 8271-80.
- Wu, J.-C.; Chen, C.-C.; Chen, K.-H.; Chang, Y.-C., Controlled growth of aligned alpha-helical polypeptide brushes for tunable electrical conductivity. *Appl Phys Lett*, 2011, *98*, 133304.
- Tsai, H.-A.; Shen, C.-N.; Chang, Y.-C., Use of surface properties to control the growth and differentiation of mouse fetal liver stem/progenitor cell colonies. *Biomacromolecules*, 2012, *13*, 3483-93.
- Wu, J.-C.; Tseng, P.-Y.; Tsai, W.-S.; Liao, M.-Y.; Lu, S.-H.; Frank, C. W.; Chen, J.-S.; Wu, H.-C.; Chang, Y.-C., Antibody conjugated supported lipid bilayer for capturing and purification of viable tumor cells in blood for subsequent cell culture. *Biomaterials*, 2013, *34*, 5191-9.

Research Interests

Designing Biomimetic Materials for Cell-Materials Interaction

My research focus aims at the design for the construction of a supramolecular architecture consisting of biomolecules or biomimetic materials. In particular, we designed and synthesized materials on mediating materials-cell interactions to select, purify, and maintain rare cells such as stem cells in primary culture and circulating tumor cells in blood. These cells are important, however, are extremely rare and hard to control. By incorporating our knowledge in biology and tools in materials interfaces and engineering, we may take one step further in controlling these rare cell systems in high precision both spatially and temporally through microfluidics or arrays. We have previously demonstrated that we were able to purify and maintain pulmonary stem/progenitor cells by nanostructures of collagen I fibrils (Huang et al, Biomaterials, 2010), or fetal liver stem cell colonies by surface physical properties (Tsai et al, Biomacrmolecules, 2010 & 2012). We have also demonstrated that by employing supported lipid bilayer as the background layer while tethering extracellular matrices, the binding specificity of cell-surface can be greatly promoted (Huang et al, Biomacromolecules, 2010, Biomaterials 2010; Tseng et al, Biomacromolecules, 2012; Wu et al, Biomaterial, 2013).



設計仿生材料並用於細胞 - 材料交互作用的研究

我的研究重點旨在利用模仿生物分子組裝的概念設計超分子結構。我們設計並合成材料並且研究材料與細胞的相互作用以利於選擇，純化和保持稀有細胞，例如幹細胞的原代培養物和血液中的循環腫瘤細胞。這些細胞是重要的，但是非常稀少且很難控制。通過整合生物學和材料界面工程，我們可更進一步利用高精度微流體或生物晶片控制這些稀少細胞。

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Education and Positions

- Ph.D., Institute of Computer and Information Science, National Chiao Tung University, 1998
- Postdoctoral Fellow, Institute of Biomedical Sciences, Academia Sinica (military service), 1998-2003
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, 2003-2007
- Associate Research Fellow, Genomics Research Center, Academia Sinica, 2007-2014
- Research Fellow, Genomics Research Center, Academia Sinica, 2014-present

Honors

- Academic Paper Awards of the Image Processing and Pattern Recognition Society, 1998
- Academia Sinica Post-doctoral Fellowship, 1999-2000
- Postdoctoral Researcher Award of National Health Research Institutes, 2001
- Academia Sinica Research Award for Junior Research Investigators, 2007
- Wu Ta-You Memorial Award, National Science Council, 2007
- Pius XI Medal, the Pontifical Academy of Sciences, Vatican, 2012

Selected Publications

- Chuang, T. J.; Lin, W. C.; Lee, H. C.; Wang, C. W.; Hsiao, K. L.; Wang, Z. H.; Shieh, D.; Lin S. C.; Ch'ang L. Y., A complexity reduction algorithm for analysis and annotation of large genomic sequences. *Genome Res,* 2003, *13*, 313-22.
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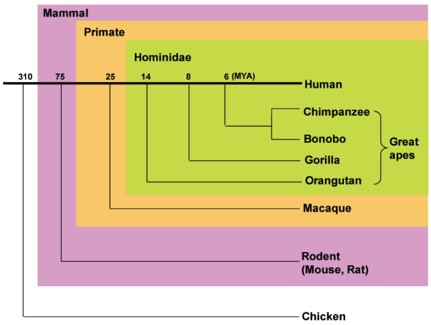
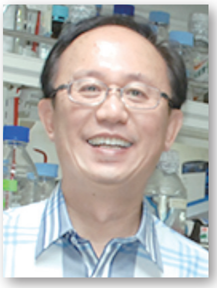
Research Interests

- **Bioinformatics**
- **Comparative & Evolutionary Genomics/Transcriptomics**
- **Post-transcriptional Regulation**
- **Big Data Analysis**
- **Systems Biology**

The goal of our studies is to comprehensively probe the transcriptome complexity and evolution across species (especially human vs. other non-human primates). It has been recognized that post-transcriptional mechanisms such as *cis-*/*trans*-splicing, circular RNA and RNA editing can generate many different transcript isoforms from the same genes, increasing the complexity of transcriptome/proteome. Despite the small genetic differences, human and other primates exhibit fairly different phenotypes. Therefore, comparative genomics/transcriptomics analyses between human and non-human primates may not only increase our understanding of human (or primate) evolution but also radiate some light on the molecular mechanisms underlying such differences between primates in disease susceptibility. Recently, the next-generation sequencing (NGS) technologies have been demonstrated to have the tremendous power of both profiling coverage and quantitative accuracy in genomics and transcriptomics studies. Based on NGS data, we analyze transcriptome/genome variations (diversity/divergence) and try to shed light on decryption of different "RNA codes" in primates.

我們設計演算法分析大量生物分子所攜帶的訊息，以期將複雜的生物資料轉變為可運用的知識，並以生物實驗驗證我們的預測與分析結果，進而協助我們瞭解各種生命現象的運作機制。本實驗室致力於基因體和轉錄體跨物種間比較與演化等生物相關研究課題，特別著重於探討靈長類動物在後轉錄修飾如 *cis-*/*trans-*splicing、RNA editing、circular RNA、long non-coding RNA 等。我們藉由 NGS 資料，以胚胎幹細胞及其分化細胞為研究平台，探討人類和其他靈長類在胚胎發育過程中的差異。另外我們也探討各種 biological factors 對演化速率的影響。





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Education and Positions

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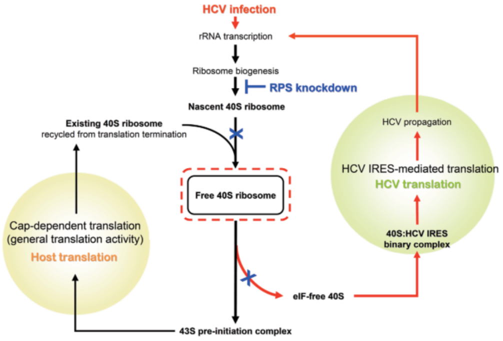
- Postdoctoral Fellow, California Institute of Technology, 1986-1991
- Assistant Professor through Associate Professor, Ohio State University, 1991-2006
- Associate Research Fellow, Genomics Research Center, Academia Sinica, 2006-present

Honors

- Genetic Graduate Group Predocotoral Fellowship, 1984
- Merck Sharp & Dohme Laboratories Postdoctoral Fellowship, 1988
- OSU Comprehensive Cancer Center Starter Cancer Research Award, 1991
- US NIH Shannon Award, 1993
- US NIH F.I.R.S.T. Award, 1994
- US NSF SGER Award, 1995
- Ohio State University College of BioSci “Outstanding Teacher Award”, 1999
- Ohio State University College of BioSci. Dean’s Award for “Best Classroom Teaching”, 2005
- Academia Sinica Thematic Project Award, 2009
- Academia Sinica Thematic Project Award, 2014
- Academia Sinica TIGP “PI of the Month” Award, 2014



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Research Interests

DExD/H-box RNA Helicases, Splicing, and Transcription-and-Splicing Coupling. DExD/H-box proteins, conventionally known as RNA helicases or RNA unwindases, are ubiquitous. They are involved in essentially all RNA-related biological processes such as mRNA splicing, ribosomal biogenesis, mRNA export, translation, and RNA turnover. We have systematically examined the roles of many DExD/H-box proteins in yeast using a combination of genetic, molecular biological, biochemical, bioinformatic, and cell biological approaches. In particular, our study on Prp28p revealed that DExD/H-box proteins function most likely as “RNPases” to “re-configure” various RNP complexes, thus playing key roles in governing the itinerary and functionality of the genetic information packages, from cradle to grave. We have since defined how Prp28p mechanistically performs its RNPase activity *vis-à-vis* the spliceosome. This pioneering research allowed us to, for the first time, capture a DExD/H-box protein in action.

Drug Discovery for anti-HCV Compounds. Hepatitis C virus (HCV) is a blood-transmitted virus that causes chronic liver diseases threatening roughly two percent of the world’s population. So far, there is no HCV vaccine and current therapies are only effective in a fraction of infected patients. We used RNAi technology to systematically search for host-cell components that HCV must employ to successfully reproduce itself. This search led to the finding that, by reducing the level of the 40S ribosomal subunit in half, HCV replication can be significantly repressed without negatively impacting on the cell health. Because ribosomal 40S subunit has been perfected over millions of years of evolution, it is extremely unlikely to morph or mutate as freely as viruses. Our finding thus opens up a new avenue for developing anti-HCV therapeutics.

張典顯研究團隊長期致力於探討 RNA 旋解酶作用的分子機制。RNA 旋解酶 (或稱為 DExD/H-box 蛋白) 是遺傳訊息由 RNA 傳遞到蛋白質過程中最具關鍵作用的蛋白。目前最新的理論認為 DExD/H-box 蛋白像是一種 RNA 蛋白酶 (RNPase)，作用在重組與 RNA 結合的蛋白上。以這種觀點來看，DExD/H-box 蛋白在遺傳訊息表達途徑上的功能，則是在於重組了在不同過程中與 RNA 結合的蛋白。儘管如此預測，這些蛋白如何執行他們的生化功能仍然是一個未解的謎。我們的長期目標是想要了解 (1) DExD/H-box 蛋白究竟是如何決定特定核醣核蛋白結構的重組，以及 (2) 他們到底又是如何系統性地整合轉錄 (transcription)、RNA 剪接、RNA 核輸出，以及轉譯的步驟。

C 型肝炎病毒是一種透過血液傳染的病毒，目前全球約有一億三千至七千萬人受其感染。當今唯一用藥對有些病毒株的治癒率不及一半，且尚無預防疫苗。我們的研究團隊運用 RNAi 的技術，逐一系統性篩選出 C 型肝炎病毒所需要的宿主細胞成份。核醣體 40S 次單元粒子中的成份就從這個篩選中脫穎而出。後續一系列的實驗證明在正常狀態下，細胞內核糖體的次單元粒子供給充沛，足夠讓細胞與 C 型肝炎病毒共用，因之 C 型肝炎病毒可以進行複製；一旦核糖體的次單元粒子短缺，此時 C 型肝炎病毒競爭不過宿主細胞的取用，其複製力因而隨之大幅下降。這個研究的一個重要意義在於：核醣體在生命演化史已存在久遠，產生變異的機會極小，若以其作為研究對抗 C 型肝炎病毒的一個標的，找到的藥物或將有其更穩定與長效之優點。

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Education and Positions

- Ph.D., Microbiology, University of California at Davis, CA USA, 1991
- Postdoctoral Fellow, Harvard Medical School, MA USA, 1993-1996
- R&D Scientist, Bio-Rad Laboratories, Hercules, CA USA, 1996-1998
- Research Scientist, Genome Institute of Singapore, Singapore, 2002-2008
- Associate Professor, NYMU (2008-present) / NTU (2011-present) / NCU (2007-present)
- Associate Research Fellow, Genomics Research Center, Academia Sinica, Taiwan, 2008-present

Selected Publications

- The FANTOM Consortium (Carninci, P.; Kasukawa, T.; Katayama, S.; et al.) The transcriptional landscape of the mammalian genome. *Science*, 2005, *309*, 1559-63.
- Chiu, K.-P.; Wong, C.-H.; Chen, Q.; Ariyaratne, P.; Ooi, H. S.; Wei, C.-L.; Ken Sung, W.-K.; Ruan, Y., PET-Tool: a software suite for comprehensive processing and managing of Paired-End diTag (PET) sequence data. *BMC Bioinformatics*, 2006, *7*, 390.
- The ENCODE Project Consortium. (Birney, E.; Stamatoyannopoulos, J. A.; Dutta, A.; et al.) Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature*, 2007, *447*, 799-816.
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- Chang, H.-J.; Jian, J.-W.; Hsu, H.-J.; Lee, Y.-C.; Chen, H.-S.; You, J.-J.; Hou, S.-C.; Shao, C.-Y.; Chen, Y.-J.; Chiu, K.-P.; Peng, H.-P.; Lee, K. H.; Yang, A.-S., Loop-sequence features and stability determinants in antibody variable domains by high-throughput experiments. *Structure*, 2014, *22*, 9-21.

Patents

- 2013/04/23 US 8428882. Chiu, K.P. et al. Methods of processing and/or genome mapping of diTag sequences.
- 2013/06/03 US 8481699. Chiu, K.P. Multiplex barcoded Paired-End ditag (mbPED) library construction for ultra high throughput sequencing.
- 2014/09/09 US 8829172. Chiu, K.P. et al. Novel multiplex barcoded Paired-End Ditag (mbPED) sequencing approach and its application in fusion gene identification.

Book

- Chiu, K.-P. DNA sequencing and sequence data analysis.

Research Interests

My research focuses on three major areas: 1) development of biotechnologies, 2) cancer research, and 3) genome sequencing of Taiwanese macaque.

Biotechnologies play a key role in biological investigations. We have developed mbPED to facilitate DNA sequencing and the study of gene expression/regulation. Besides, TOP-PCR is a robust approach capable of amplifying trace amount of DNA for genome-wide identification of remote cancer mutations. Cancer research aims to employ novel technologies to enhance the identification of cancer mutations and use sequencing to analyze the mechanisms of interaction between anticancer drugs and cancer cells, so to facilitate the search of drug targets. For example, for the first time, we've found that *A. cinnamomea* (牛樟芝) was able to collapse the miRNA system of cancer cells within hours, suggesting that proteins/genes involved in miRNA biogenesis and/or maturation pathways can be valuable drug targets for cancer treatment. Taiwanese macaque (*Macaca cyclopis*), the only nonhuman primate endemic to Taiwan, has a strong potential for the study of primate evolution and medical applications. Genome sequencing of *M. cyclopis* aims to sequence, assemble and annotate both of its mitochondrial and nuclear genomes.

我的研究主題主要有三：1)生物科技的研發，2)癌症研究，以及3)台灣獼猴的基因體定序。

生物科技在生物學的研究上扮演著關鍵性的角色。我們已開發出mbPED用以加速DNA定序以及在基因表達與調控上的研究。另外，TOP-PCR則以最有效的方式擴增微量的DNA，可以全基因體地偵測遠端癌症病變。癌症研究的目的在於利用新科技以加速識別癌基因突變，並使用定序來分析抗癌藥物與癌細胞之間的作用機制，以識別藥物標靶。例如，史上首例，我們發現牛樟芝可以在幾小時內全面地瓦解癌細胞內的微核糖核酸（miRNA）系統，顯示參與微核糖核酸製造與 / 或成熟過程的蛋白質或基因可以是治癌標靶。台灣獼猴 (*Macaca cyclopis*) ，島上除了人類以外唯一的靈長類動物，在靈長類演化與醫學的研究上甚具價值。台灣獼猴基因體定序的目的在於定序 (解讀)、組裝、與基因定位台灣獼猴在粒腺體內以及在細胞核內的兩組基因體。

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Education and Positions

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- Postdoctoral Fellow, Academia Sinica, 2001-2005
- Postdoctoral Fellow, Natl. High Mag. Field Lab., Florida State University, 2002-2003
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, 2005-2011
- Associate Research Fellow, Genomics Research Center, Academia Sinica, 2011-present

Honors

- Outstanding Students Conference Travel Grant, The Foundation for the Advancement of Outstanding Scholarship, Taiwan, 2000
- Outstanding Post-Doctoral Researcher Conference Travel Grant, The Foundation for the Advancement of Outstanding Scholarship, Taiwan, 2002 and 2004
- Advanced Abroad Research Fellowship, The National Science Council of Taiwan, 2002-2003
- Young Researcher Award, The Taiwan Society for Mass Spectrometry, 2011
- Career Development Award, Academia Sinica, 2012

Selected Publications

- Tsai, S.-T.; Chen, C.-W.; Huang, L.-C.; Huang, M.-C.; Chen, C.-H.; Wang, Y.-S., Simultaneous mass analysis of positive and negative ions using a dual-polarity time-of-flight mass spectrometer. *Anal Chem*, 2006, *78*, 7729-34.
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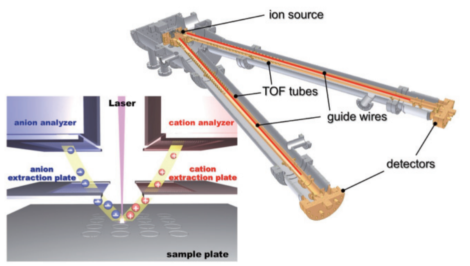
Research Interests

Instrumentation and Biophysics

Our laboratory has aimed at advancing biological and analytical sciences with new tools and methods. To pursue the challenges, we have developed several novel mass spectrometric techniques complementarily for basic research and analytical purposes. In the basic research, the detail ionization chemistry of biological samples is analyzed, and the results are used to develop mass spectrometric methods for efficient carbohydrate analysis. For the analytical studies, a comprehensive ion detection method is developed for molecular imaging of tissue sections or plant samples without signal loss. A further advancement is the development of new ionization system for the molecular imaging in the cellular level with ultrahigh spatial resolution Aside from the development of mass spectrometric methods, the midterm perspective of our laboratory is to develop efficient and convenient sample diagnostic methods in ambient and liquid conditions.

以有效的物理化學方法研發新的生化分析及檢測技術，是我們近年的主要研究方向。我們已發展數個新穎質譜技術，可同時用於基礎研究及改善分析效率。可檢測完整離子訊號的同步雙電性質譜法是其中一例，可避免傳統技術無法克服離子電性選擇的缺點。同步雙電性檢測法對於檢測複雜多變的生物樣品檢測極為重要，尤其是分子影像及樣品游離反應的研究。由於新的質譜技術可提供多於傳統質譜技術的資訊，使得我們可更瞭解樣品檢測的困難及限制。因此，針對醣分子的檢測技術開發可以在更確實的實驗基礎下進行，也是我們目前的重點實驗方向之一。除了傳統質譜技術的開發之外，我們也全力開發更新穎且簡便的樣品檢測技術，期望在大氣以及液態環境中提供接近於質譜儀的功能與準確度。

synchronized dual-polarity mass spectrometer for comprehensive molecular imaging



Biotechnology Incubation Center

The Biotechnology Incubation Center (BIC) is established for the purpose of fully utilizing the scientific strength, international connections and resources of Acadmia Sinica to assist start-up companies to commercialize the research outcomes of Academia Sinica (AS).

All domestic and international biotechnology companies are welcome to license AS technologies and join BIC to develop new drugs and tools. By providing technical counsel, business development expertise and managerial support, we aim at facilitating the marketing of the products derived from AS proprietary technologies to accelerate the growth of portfolio companies to become the future stars of the biotech industry. Through these endeavours, we hope to achieve superior economic outcomes by increasing job opportunities, improving infrastructure and facilitating the establishment of a prosperous bio-pharmaceutical industry in Taiwan.

- **Straightforward Strategy**

BIC assists the growth of new ventures engaging in the development of innovative technologies and pharmaceutical products.

- **Convenient Location**

Located within the Nankang Software Park, BIC is just 1.5 km from the Academia Sinica campus. A flexible space of 88,000 square feet is available for portfolio companies to set up laboratories and offices.

- **Excellent Development Environment**

Academia Sinica conducts lecture series and collaborates with research institutes locally as well as internationally. Portfolio companies are welcomed to participate in these activities. With the backing of Academia Sinica's substantial knowledge base, portfolio companies have easy access to renowned scientists with whom they can exchange ideas and/or establish research collaborations.

- **Creative Science and Technology**

Academia Sinica has many discoveries and technologies awaiting development and commercialization. Portfolio companies at BIC have first-hand access to these technologies and priority in gaining collaboration and licensing opportunities.

- **Comprehensive Support**

BIC offers access to a wide range of research resources available at Academia Sinica. BIC is supported by an extensive group of scientists with a broad spectrum of expertise available for collaboration and/or consultation. Selected research instruments are accessible on the premises and available to portfolio companies to use at will. BIC also provides general administrative support, including facility maintenance, library services and professional consultation. Managers are on-site to provide strategic and/or operational consultation.

生技育成中心

生技育成中心的主要任務是利用我們在國內外豐沛的人脈關係、科技研發能量以及資源協助育成新創公司，將本院與生技醫藥尤其是基因體有關的重要研究與發明產業化。

我們歡迎國內外具有高度潛力的生技製藥公司或團隊技術移轉本院之創新技術並進駐生技育成中心。本中心會透過技術、策略、及管理之各項協助，促進進駐廠商與中央研究院共同合作，開發新技術與新產品，並輔導進駐之新創公司成為新生物技術、新藥開發或新精密儀器的明日之星，以達成本中心協助產業升級、創造就業機會，促進台灣生技製藥產業的深耕與發展之主要目標。

- **策略一貫**

以新創生技及新藥開發公司為主，加速研發成果產業化。

- **空間適中**

設立在南港軟體園區內；含公共設施共有面積 2,500 坪，可以提供足夠空間組合之彈性，供廠商設立實驗室及辦公室。

- **環境良好**

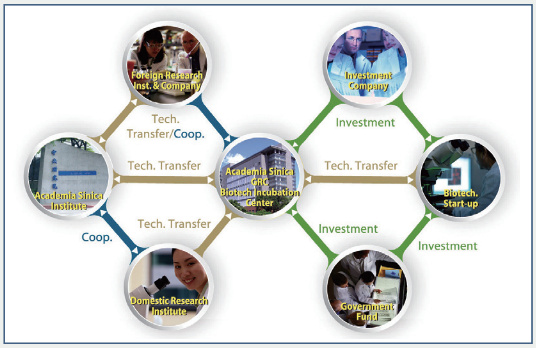
生技育成中心為中央研究院基因體研究中心附屬單位，具有高水準的技術資源為後盾，包括特殊儀器、專題講座、訓練課程等。本院與國內外生物醫學產業研究機構之交流合作密切，進駐廠商可參與院內舉辦的國際性活動，增加與國內外專家學者互動。

- **科技創新**

廠商得優先探勘本院所擁有的多項專利技術，經由公共事務組取得技術移轉或研究合作機會。

- **全面服務**

提供一般行政、專業諮詢、圖書、資訊等各項支援服務，並提供廠商付費使用的貴重儀器設施，及研發諮詢與合作。



Chi-Ming Liang 梁啓銘

Distinguished Research Fellow and Division Director of Biotechnology Incubation Center

特聘研究員兼生技育成中心執行長

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Education and Positions

- B.S., Pharmacy, National Taiwan University, Taiwan, 1970
- M.S., Chemistry, National Taiwan University, Taiwan, 1973
- Ph.D., Pharmacology, University of Arkansas for Medical Sciences, 1977
- Fogarty Visiting Fellow, National Institutes of Health, 1977-1980
- Senior Staff Fellow, National Institutes of Health, 1980-1982
- Head of Immunology, Biogen S.A., 1982-1986
- Senior Scientist, Biogen Research Corp., 1986-1987
- Acting Chief, Immunology Section, Retrovirology Branch, Division of Blood & Blood Products, FDA, 1987-1990
- Director of Molecular Immunology, Oncologix Inc.,1990-1994
- Scientific Director, Assayland, Inc., 1994-1997
- Director, Office of Public Affairs and Technology Transfer, Academia Sinica, 1997-2006
- Research Fellow, Institute of Biological Chemistry, Academia Sinica, 1997-2006
- Distinguished Investigator & Secretary General, National Health Research Institutes, 2006-2009
- Director, Office of Public Affairs, Academia Sinica, 2009-2013
- Distinguished Research Fellow, Genomics Research Center, Academia Sinica, 2009-present
- Division Director, Biotechnology Incubation Center, Genomics Research Center, Academia Sinica, 2009-present

Honors

- Outstanding Alumnus Award, School of Pharmacy, National Taiwan University, 2008
- Model Civil Servant, Academia Sinica, 2011

Selected Publications

- Kuo, C.-C.; Lin, W.-T.; Liang, C.-M.; Liang, S.-M., Class I and III phosphatidylinositol 3’-kinase play distinct roles in toll-like receptor signaling pathway. *J Immunol*, 2006, *176*, 5943-9.
- Kuo, C.-C.; Liang, S.-M.; Liang, C.-M., CpG-B ODN promotes cell survival via up-regulation of heat-shock protein 70 to increase Bcl-xL and to decrease apoptosis-inducing factor translocation. *J Biol Chem*, 2006, *281*, 38200-7.
- Kuo, C.-C.; Liang, C.-M.; Lai, C.-Y.; Liang, S.-M., Involvement of Hsp90βbut not Hsp90α in anti-apoptotic effect of CpG-B ODN. *J Immunol*, 2007, *178*, 6100-8.
- Yang, C. D.; Liao, J. T.; Lai,C. Y.; Jong, M. H.; Liang, C.-M.; Lin, Y. L.; Lin, N. S.; Hsu, Y. H.; Liang, S.-M., Induction of protective immunity in swine by recombinant bamboo mosaic virus expressing foot-and-mouth disease virus epitopes. *BMC Biotechnol*, 2007, *7*, 62-70.
- Huang, C. Y.; Liang, C.-M.; Chu, C. L.; Liang, S.-M., Albumin fibrillization induces apoptosis via integrin/FAK/Akt pathway, *BMC Biotechnol*, 2010, *9*, 2009
- Peng, J.-M.; Chen, Y.-H.; Hung, S.-W.; Chou, C.-F.; Ho, M.-Y.; Lee, Y.-J.; Lai, T.-C.; Hsiao, M.; Liang, C.-M.; Liang, S.-M., Recombinant viral protein promotes apoptosis and suppresses invasion of ovarian adenocarcinoma cells by targeting α5β1 integrin to downregulate Akt and MMP-2. *Br J Pharmacol*, 165: 479-93.
- Cheng, Y. T.; Chen, T.A.; Chen C. Y.; Liang, C.-M.; Liang, S.-M., 3’poly-G—tailed ODNs inhibit F-spondin to induce cell death and neurite retraction in rat embryonic neurons *Mol Neurobiol*, 2012, *45*, 536-49.

- Liao, C. C.; Ho, M. Y.; Liang, S.-M.; Liang, C.-M., Recombinant protein rVP1 upregulates BECN1-independent autophagy, MAPK1/3 phosphorylation and MMP9 activity via WIPI1/WIPI2 to promote macrophage migration. *Autophagy*, 2013, *9*, 5-19.
- Ho, M. Y.; Liang, S.-M.; Hung, S. W.; Liang, C.-M., MIG-7 controls COX-2/PGE2 mediated lung cancer metastasis. *Cancer Res*, 2013, *73*, 439-49.
- Chiu, C. F.; Ho, M. Y.; Peng, J. M.; Hung, S. W.; Liang, C. M.; Liang, S.-M., Raf activation by Ras and promotion of cellular metastasis require phosphorylation of prohibitin in the raft domain of plasma membrane. *Oncogene*, 2013, *32*, 777-87.

Patents

- Liang, S.-M.; Huang, C. Y.; Liang, C.-M., 2010, Method of producing fibrillar proteins. GB 2460283.
- Liang, S.-M.; Huang, C.Y.; Chen, Y.P.; Liang, C.-M., 2012, Process to produce fibrillar proteins US 8268974.
- Liang, S.-M.; Liang, C.-M., 2013, Anti-tumor fibrillar human serum albumin methods and composition US 8357652.
- Liang, S.-M.; Peng, J.-M.; Liang, C.-M., 2013, Apoptosis-inducing polypeptides. EP Patent No. 2,465,531B1.

Research Interest

My research interests are mainly in the fields of immune and vaccine development as well as cancer metastasis and treatments. While I worked at Biogen, a leading biotechnology company during, I participated in many projects and helped the successful development and marketing of two multi-billion dollars drugs, i.e., alpha and beta-inteferon for Biogen. I was the first to produce anti-TNF monoclonal antibodies, which turned out to be a multi-billion dollars drug too. I came back to Taiwan in 1997, serving as the Director of Office of Public Affairs (Technology Licensing) Academia Sinica and helped Academia Sinica to sign more than NT$2 billion of licensing contracts. I have also been responsible for supervising Biotechnology Incubation Center (BIC) of Academia Sinica. The BIC has a facility of around 90,000 square feet which is occupied by 9 portfolio companies with capital of more than NT$14 billion and 20 products in clinical trials. In addition, I have served as a scientific and technology licensing consultant for many Taiwanese government branches including National Science Council, Ministry of Economic Affairs, Department of Health, National Defense Medical College and National Taiwan University etc., to help the build-up of biotechnology and pharmaceutical industry in Taiwan through focusing on profitable projects and establishment of a stream-line cooperation system among government institutes, universities and bio-pharmaceutical industry.

我實驗室主要進行免疫、疫苗及癌症轉移治療相關研發。我曾參與 alpha- 干擾素、beta- 干擾素及 anti-TNF 抗體等產品的研發及商化，這些產品至今的銷售額達千億美金。我在 1997 年回國，除了研究，尚協助中研院設立智財管理與推廣部門，並督導生技育成中心，努力促進產官學研合作，期望有助於我國生技製藥產業的快速發展及起飛。

Research Specialists

Chi-Fon Chang 張七鳳

Senior Research Specialist
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Education and Positions

- Ph.D., Biophysics, The Ohio State University, 1997
- Postdoctoral Fellow, Institute of Biomedical Sciences, Academia Sinica, 1997-1999
- NMR Supporting Team Manager, Institute of Biomedical Sciences, Academia Sinica, 1999-2002
- NMR Facility Manager, High-Field NMR Center, Academia Sinica, 2002-present
- Associate Research Specialist, Genomics Research Center, Academia Sinica, 2004-2010
- Senior Research Specialist, Genomics Research Center, Academia Sinica, 2010-present

Expertise

As a research specialist, I am responsible for the daily operation on NMR facility and assist researchers carrying out NMR related researches. I have dedicated myself to provide competent and efficient routine service, as well as all aspects of advance technical support on NMR spectroscopy. The duty of my job includes: keeping track of machine time usage; supervising the facility staff members; training users on using NMR spectrometers; developing and implementing new NMR experiments; assisting users setting up advanced NMR experiments; advising users on specific NMR experiments and applications; and providing technical consultation. My expertise is using biophysical methods, especially the NMR approach, to obtain structural and functional information for biomolecules. Recently, we have also set up protocols for fragment-based screening using NMR.

主要負責管理基因體中心核磁共振核心實驗室及院內高磁場核磁共振核心，並參與或支援研究人員核磁共振相關研究。服務內容包括：管理核心工作小組確保核心軟硬體正常運作；調控核心所有儀器的時間分配；提供使用者技術及實驗規劃之諮詢；協助蒐集分析圖譜；訓練新進使用者；舉辦教育訓練課程；發展或引進核磁共振相關新技術；參與核磁共振相關研究計畫。

Ting-Jen Rachel Cheng 鄭婷仁

Senior Research Specialist
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tingjenc@gate.sinica.edu.tw

Education and Positions

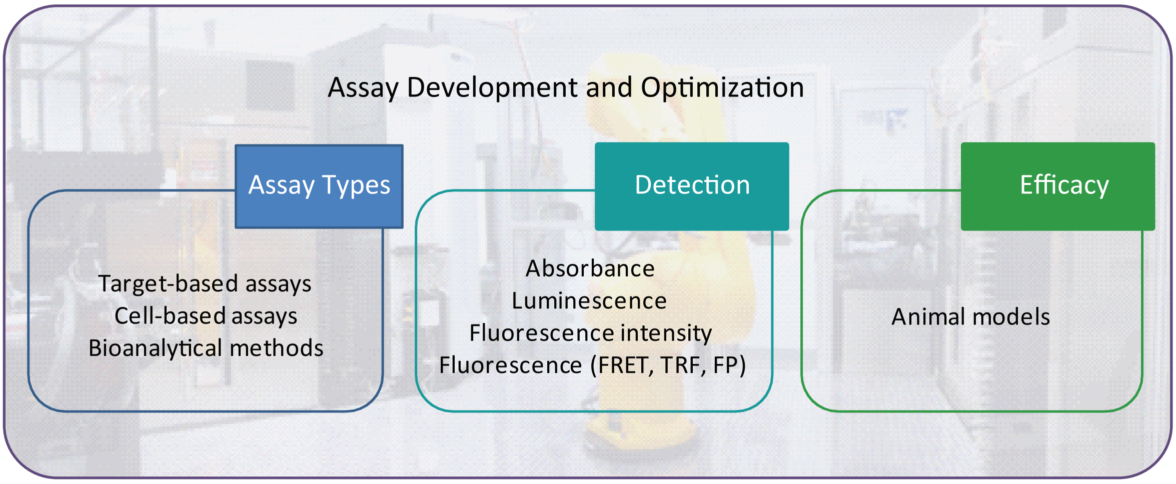
- B. Eng., Chemical Engineering, National Tsing Hua University, 1993
- Ph.D., Life Sciences, National Tsing Hua University, 1999
- Postdoctoral Fellow, Keck Graduate Institute, 2000-2005
- Assistant Research Specialist, Genomics Research Center, Academia Sinica, 2005-2008
- Associate Research Specialist, Genomics Research Center, Academia Sinica, 2008-2012
- Research Specialist, Genomics Research Center, Academia Sinica, 2012-present

Expertise

Assay development for functional evaluation and high-throughput screening

The main focus of my role in the Genomics Research Center is to support assay needs in the PI-initiated and the theme projects. The bio-assay platforms can be developed for functional evaluation of the small molecule(s) or the protein(s) of interest and for high-throughput screening to identify potential leads for drug discovery. The current duties include: (1) target-based assay development with recombinant proteins and molecular probes, such as enzymatic reactions or protein binding studies, etc., (2) cell-based assay development with reporters, (3) high-throughput screening to identify potential hits, (4) activity evaluation of the small molecules as well as natural products, and (5) efficacy evaluation of vaccines and small molecules.

主要支援基因體中心研究團隊對活性分析的需求；例如針對有興趣的藥物標的建立生化分析及活體內活性分析系統並執行藥物篩選。目前的協助範圍包含了 (1) 設計並建立發展藥物標的之生化活性偵測系統，如酵素反應以及蛋白質結合能力測試等，(2) 設計藥物標的之細胞內活性偵測系統來決定化合物在活體內之活性，(3) 設計適合高速篩選的活性分析平台並執行高速藥物篩選選擇具活性之化合物，(4) 評估及測試小分子及天然化合物的生物活性，以及 (5) 評估疫苗及小分子在活體內的效果等。



Yin-Chu Chien 簡吟曲

Senior Research Specialist
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Education and Positions

- Ph.D., Epidemiology, National Taiwan University, 2003
- Senior Specialist in Minister's Office, Department of Health, 2003-2005
- Postdoctoral Research Fellow, Graduate Institute of Epidemiology, National Taiwan University, 2005-2006
- Senior Specialist in Minister's Office, National Science Council, 2006-2008
- Postdoctoral Research Fellow, Genomics Research Center, Academia Sinica, 2008-2011
- Visiting Assistant Professor, Department of Pediatrics and Human Development, MSU College of Human Medicine, USA, 2009
- Associate Research Fellow, Molecular and Genomic Epidemiology Center, China Medical University Hospital, 2011-2014
- Senior Research Specialist, Genomics Research Center, Academia Sinica, 2014-present

Honors

8th Chen Kong-Pei Best Public Health Paper Award, 陳拱北教授最佳論文獎 2002

Expertise

Research and Management of the Health Cloud Research Program

Taiwan's National Health Insurance (NHI) program has been considered as one of the most successful program in the past twenty years since the program was launched in 1995. This nationwide program provides medical and healthcare services with the highest coverage rate, most comprehensive welfare, and the highest accessibility than any other health insurance programs in the world. There are increasing amount of research using sampling data from the NHI claims database have been published. It is extremely important to carry out a multidisciplinary study to integrate these nationwide scaled databases such as household registry, cancer registry, death certification, national screening projects, Taiwan Biobank, and national health insurance to construct a nationwide health database with high quality and accuracy of data. I take in charge the Research and Management of the Health Cloud Research Program in Academia Sinica. The goal of the program is to set up a National Big Health Data Center in Academia Sinica. I have good experiences in the management and analysis of large scaled health data, and have some publications in high-impact journals. I am interested in the research of applications with nationwide scaled dataset for health improvement.

主要負責中央研究院「健康雲跨領域研究：巨量健康資訊科技之研發與應用」計畫，協助規劃籌設本院「健康雲跨領域研究中心」，在維護基本人權、保護個人隱私以及確保資訊安全之狀況下，逐步於研究中心設置「全國健康巨量資料庫」，訂定相關保密及安全規範，強化健康研究中心之資訊安全與作業人員管制，提供全國學研界不具個人識別資訊之健康巨量資料，以進行健康相關研究與醫藥開發。

Shaouyen Liu 劉小燕

Senior Research Specialist

研究技師

shaouyen@gate.sinica.edu.tw

Education and Positions

- B.S., Applied Mathematics, Tsing Hua University, 1978
- M.S., Computer Science, University of Houston, 1981
- Software Engineer, Institute of Information Industry, Taipei; Allstate Life Insurance Company, IL, USA; Texaco Inc., TX, USA, 1982-1993
- Various Managerial Positions, Moderntimes Financial Information Co.; Netbiz Software Information Service Inc.; Syspower Inc.; DTC Cortex Consulting, 1993-2003
- Associate Research Specialist, Genomics Research Center, Academia Sinica, 2003-2010
- Senior Research Specialist, Genomics Research Center, Academia Sinica, 2010-present

Expertise

The Information Unit in GRC is responsible for providing services regarding Information Technologies as well as Science Communications to ensure a reliable and 7x24 available e-environment to support scientific research work.

The IT aspect duties include:

- Providing a reliable and up-to-date e-environment for scientific research in GRC
- Maintenance of scientific computing facilities, data storages
- Enforcing information security policies
- Providing services to provide integrated administrative application systems for enhancing workflows and leveraging e-technology

The Science Communications duties include:

- Productions and coordination of scientific news announcements
- Promotion of research achievements through new media technologies

主要負責基因體中心資訊組之管理與統籌，涵蓋資訊服務及媒體通訊事宜。

資訊服務內容包括：

- 提供可靠且與時俱進的資訊環境，包括基礎建設的建置與維護、各式網路連線及電腦軟、硬體的採購、建置、維護，以及科學研討會議進行的 e 化服務
- 提供高速巨量科學運算設施及資料儲存設備之維護
- 維護資訊安全
- 推廣 e 化的行政業務系統

媒體通訊方面的任務包括：

- 科學研發媒體報導資料之製作
- 以科普、多媒體形式，推廣中心研究成果

Shi-Shan Mao 毛溪山

Senior Research Specialist

研究技師

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Education and Positions

- B.S., Chemistry, National Tsing-Hua University, 1978
- Ph.D., The Johns Hopkins University, 1987
- Postdoctoral Fellow, Massachusetts Institute of Technology, 1990
- Senior Research Fellow, Merck Research Laboratories, 2001
- Senior Research Specialist, Genomics Research Center, Academia Sinica, 2007-present

Expertise/Specialty

The combined experience in both academic and industrial provides me the foundation for both basic research and drug discovery and development. I have extensive learning in biochemistry, enzymology, natural product biosynthesis during my academic years. My current works at Academia Sinica are in two parts: helping technology transfer of Academia Sinica research discoveries and coordinating the operation and collaboration of high through-put screening.

在學術界以及工業界的雙重經驗讓我在基礎研究及新藥開發方面都有良好的根基，在學術界從事研究期間，我大量的學習到有關生物化學、酵素化學及天然物合成方面的知識，目前我在中央研究院的工作分成兩個部份：協助中研院研究成果技術移轉，以及協調高速藥物篩選計劃的運作及合作研究。

Sophia Su 蘇瑟宜

Senior Research Specialist
研究技師
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Education and Positions

- Ph.D., Integrated Program in Cellular, Molecular and Biophysical Studies, Columbia University, 1993
- Post-Doctoral Research Fellow, Department of Biophysics, Kyoto University, Kyoto, Japan, 1993-1996
- Research Fellow, National Taiwan University Hospital, Department of Internal Medicine, Center for Cardiovascular Research, 1997-1999
- Senior Consultant/ Analyst, TNS Corporate Finance Company (formerly Arthur Andersen, Global Corporate Finance Division), 1999-2002
- Director, Taian Technologies Corporation, 2002-2003
- Senior Manager, Biotechnology Incubation Center, Genomics Research Center, Academia Sinica, 2005-present
- Associate Research Specialist, Biotechnology Incubation Center, Genomics Research Center, Academia Sinica, 2007-2013
- Senior Research Specialist, Biotechnology Incubation Center, Genomics Research Center, Academia Sinica, 2013-present

Facility Management / Expertise

The Incubation Center is an outpost facility that houses a number of burgeoning biotech companies actively developing key Academia Sinica technologies into high valued commercial products. As the manager of the Biotechnology Incubation Center, my duties include managing the daily operations of the facility, and providing business development support to portfolio companies. These include supervising the staff members and monitoring the progress of the portfolio companies in order to deliver the necessary technical, financial, as well as regulatory support. In addition to serving as liaison to facilitate collaborations with life science-related companies, I am also responsible for leading my team in creating spin-off ventures as well as other commercial endeavors based on Academia Sinica technologies.

主要負責經營管理基因體中心生技育成中心及提供育成相關服務。服務內容包括：負責生技育成中心的日常實際運作；管理核心工作小組；提供育成廠商所須的技術服務、策略規劃及其他相關諮詢；統籌辦理儀器使用訓練課程、生技產業相關座談會等活動。除管理生技育成設施及相關活動外，亦支援技術移轉、輔導成立新創公司、及參與其他技術商業化相關業務。

Daisy Tsai 蔡淑芳

Senior Research Specialist, Genomics Research Center
Deputy Director General, Academia Sinica
研究技師兼中央研究院副秘書長
daisy306@gate.sinica.edu.tw

Education and Positions

- M.P.H., Epidemiology, National Taiwan University, Institute of Public Health, 1987
- Assistant Research Fellow, Institute of Biomedical Sciences (IBMS), Academia Sinica, 1987-1996
- Program Manager through Senior Program Manager, National Health Research Institutes, 1996-2003
- Deputy Director of Extramural Research Affairs Department, National Health Research Institutes, 2000-2003
- Adjunctive Executive Secretary to Academic Technology Development Program-Biomedical Study Section, Ministry of Economic Affairs, 2001-2002
- Senior Research Specialist, Genomics Research Center, Academia Sinica, 2003-present
- Deputy Director General, Academia Sinica, 2011-present

Honors and Professional Training

- Excellent Publication Award, National Science Council, 1990, 1991, 1993, and 1994 (four times)
- Special Training Program on Peer Review System at the National Institutes of Health, USA, 1994
- Established the Research Grant Review System and Post - Awarded Management System in National Health Research Institutes, Taiwan, 1995-1996

Membership

- The Society of Research Administrators International (SRA International), USA
- Academy of Management, USA

Expertise and Responsibility

My expertise is in academic strategic planning, research evaluation and management in order to facilitate and expedite the administrative flow while providing professional management service to principle investigators in the hope of meeting the needs of researchers to advance performance both locally and internationally.

- **Main responsibilities at GRC:**

  規劃與推動中心學術業務，提供學術行政之支援。

  A. Executive Secretary of Scientific Advisory Board

  B. Program management of large scale programs including Genome Summit Program of Academia Sinica, 機關首長雄才大略之政策優先計畫 , and international cooperation projects.

  C. Assist to execute special assigned cross-institutes and interdisciplinary projects within Academia Sinica.

  D. Consultation and administrative support for application of extramural research project grants, awards, and scholarship to enhance the chance for acquirement.

  E. Academic activity (conferences, symposiums, seminars, and scholars' visits) planning and management to strengthen the research advantage of GRC.

- **Duties as Deputy Director General of Academia Sinica**

  A. Assisting Director General to promote and manage administration affairs in Academia Sinica

  B. Co-chair of execution team for National Biotechnology Research Park Development Program

  C. Coordinator for the Congressional and Legislative Affairs

Ying-Ta Wu 吳盈達

Senior Research Specialist
研究技師
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Education and Positions

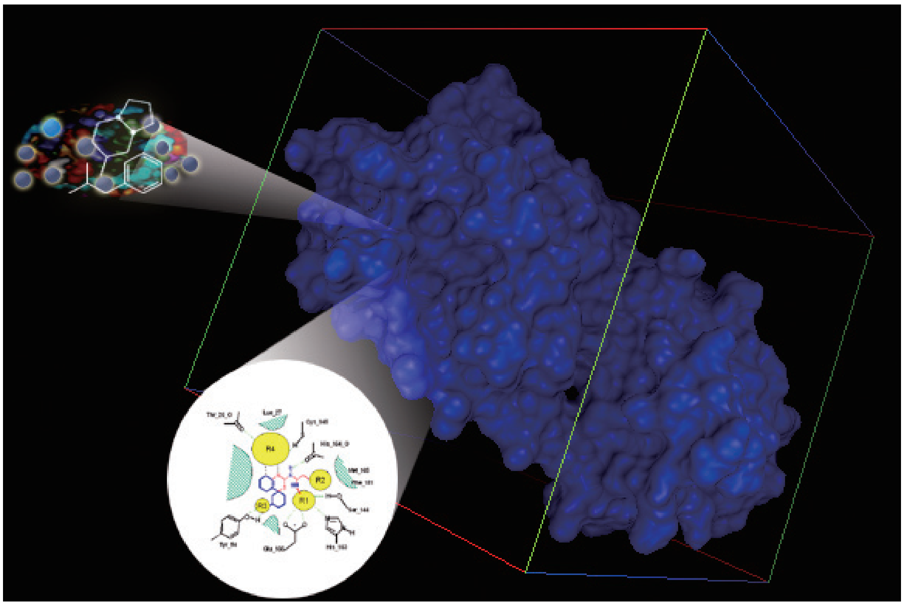
- Ph.D., Chemical Engineering Department of SUNY at Buffalo, 1990-1996
- Manager of Administrative Office of NRPGM, 2001-2004
- Postdoctoral Fellow, IBC, Academia Sinica, Taipei, 1996-2001
- Assistant Research Specialist, Genomics Research Center, Academia Sinica, Taipei, 2004-2007
- Associate Research Specialist, Genomics Research Center, Academia Sinica, Taipei, 2007-2012
- Research Specialist of Genomic Research Center, Academia Sinica, Taipei, 2012-present

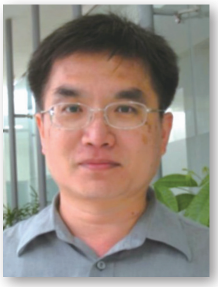
Facility Management / Expertise

Structure function to drug discovery

Our research devotes to the technology of probing biomolecular recognition and protein-drug interactions, together with the strategy for structure-based drug discovery, as a supporting component of the GRC's chemical biology research. Besides supporting experimental assay, we apply both text mining approach and computation technology to compose an integral database containing information of interaction and relationship of small molecule with targets. Our major duty, therefore, is to operate an up-to-date high-throughput screening (HTS) platform and informatics tools to assist research PIs in defining features of functional targets for drug discovery.

研究致力於開發探測生物分子間相互識別，以及生物分子與藥物間相互作用的技術，結合使用結構為基礎的藥物設計策略，用以支援中研院基因體中心進行生物化學研究。除了支援實驗，我們同時運用文字探勘方法與計算技術以整合包括小分子與疾病標的物間的相互作用與相互關係的資料庫。因此主要任務為維繫最新的高速篩選平臺與工具，以協助研究人員確定其標的物作為藥物設計目標的特徵。





Jia-Tsrong Jan 詹家琮

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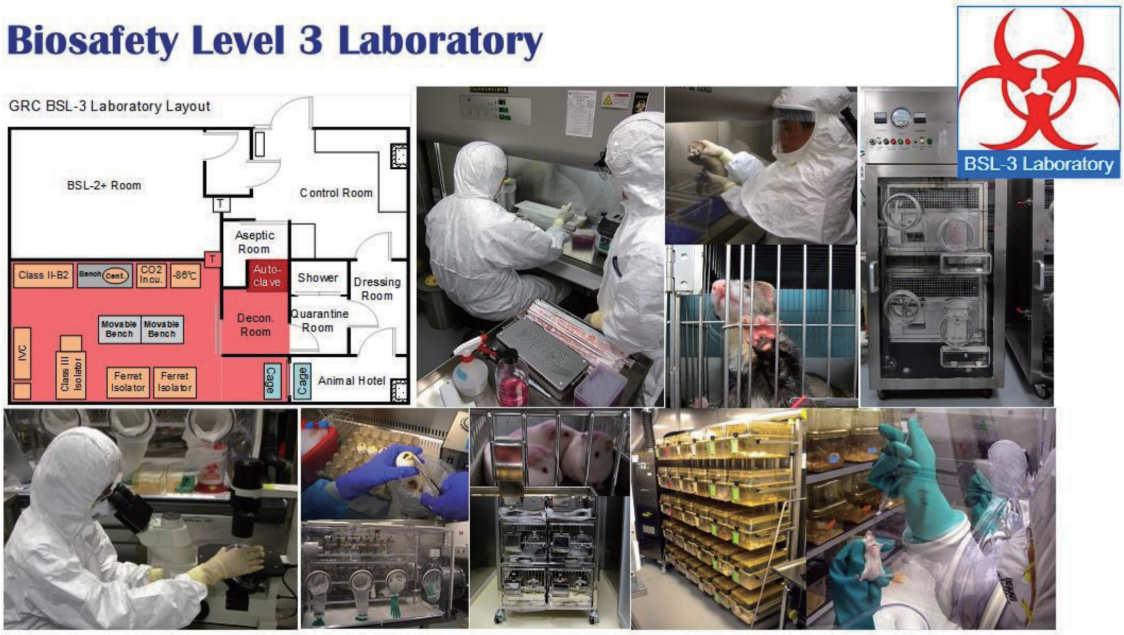
Education and Positions

- B.S., Biology, National Taiwan Normal University, 1982
- M.S., Microbiology and Immunology, National Defense Medical Center, 1985
- Ph.D., Molecular Microbiology and Immunology, Johns Hopkins University, 1998
- Research Assistant Fellow through Associate Research Fellow of Immunology, Institute of Preventive Medicine, National Defense Medical Center, 1987-2006
- Associate Research Specialist, Genomics Research Center, Academia Sinica, Taiwan, 2006-present

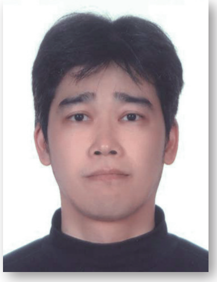
Expertise

As an associate research specialist, I am responsible for the Biosafety Level-3 (BSL-3) laboratory in GRC. This special laboratory is built to provide supportive practices for institutional researches against naturally occurring infectious microorganisms of high-risk to humans that require special containment devices, appropriate personal protective equipment, and rigorous regulations. The GRC BSL-3 laboratory has the certificate from Taiwan's Centers for Disease Control (CDC) and is well organized with experienced members and equipped with appropriate safety containments for both *in vitro* cell-based assays and *in vivo* small animal experiments.

基因體研究中心生物安全第三等級實驗室是提供安全實用的硬體設施、良好的管理與操作軟體，及具豐富經驗與熟練實驗操作的研究人員，執行本中心並協助院內其他單位高危險感染性微生物材料之研究工作。本實驗室具有細胞實驗與動物實驗功能兼備、生物安全第三與第二等級 (含＋) 實驗可交替進行、配置專職之研究團隊、對內執行研究任務，對外可提供合作服務等特性。



The Biosafety Level 3 (BSL-3) Laboratory in GRC is to provide experiment practices for institutional researches against infectious microorganisms of high-risk to humans that require special containment devices, appropriate personal protective equipments, and rigorous regulations. The BSL-3 laboratory was designed for both *in vitro* cell-based and *in vivo* small animal studies. Experimental animal models such as mice, guinea pigs, and ferrets have been established for studies of influenza viruses, including evaluation of the efficacy of influenza vaccine candidates, the effect of glycolipids as adjuvant, and the antiviral activity of natural and synthetic compounds and herbal extracts



Jung-Lee Lin 林俊利

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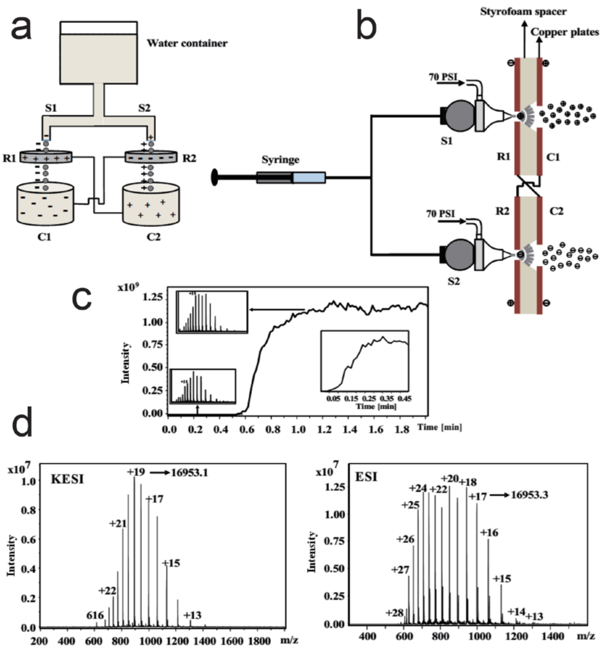
Education and Positions

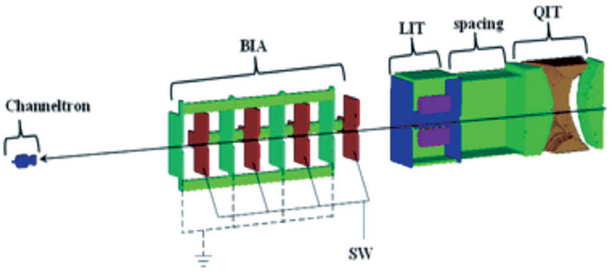
- Ph.D., Chemistry, National Taiwan University, 2002
- Postdoctoral Fellow, Institute of Atomic and Molecular Sciences, Academia Sinica, 2002-2007
- Assistant Research Specialist, Genomics Research Center, Academia Sinica, 2007-2012
- Mass Spectrometry Facility Manager, 2010-present
- Associate Research Specialist, Genomics Research Center, Academia Sinica, 2012-present

Facility Management / Expertise

Main job is responsible for the development new mass spectrometry technology and management mass spectrometry core facility in Genomics Research Center. New mass spectrometric techniques are mainly aimed at commercial mass spectrometer which mass range is not available and developed unique methods to enhance the efficiency of ionization and detection. Mass spectrometry core facilities mainly provide routine sample analysis service, proteomics and glycomics analysis, structure analysis of glycans and glycoproteins in details, software operation services, new staff training course, and to assist users in operating the mass spectrometer. Management of mass spectrometry core facility maintains facility to operate in normal condition and personnel management.

主要工作是負責開發新的質譜技術及管理基因體中心質譜儀核心設施。質譜技術開發目前主要是針對商業化質譜儀無法量測的質量範圍為主要目標，另外也研發特殊的偵測方法增加游離與偵測的效率。質譜儀核心設施主要提供例行性樣品檢測服務，質譜數據分析服務與特定分子結構分析與比對，分析軟體操作服務，新進人員質譜操作教育訓練，協助使用者操作質譜儀。管理基因體中心質譜儀核心設施主要工作是維護設施正常運作與人員管理。





Wen-Bin Yang 楊文彬

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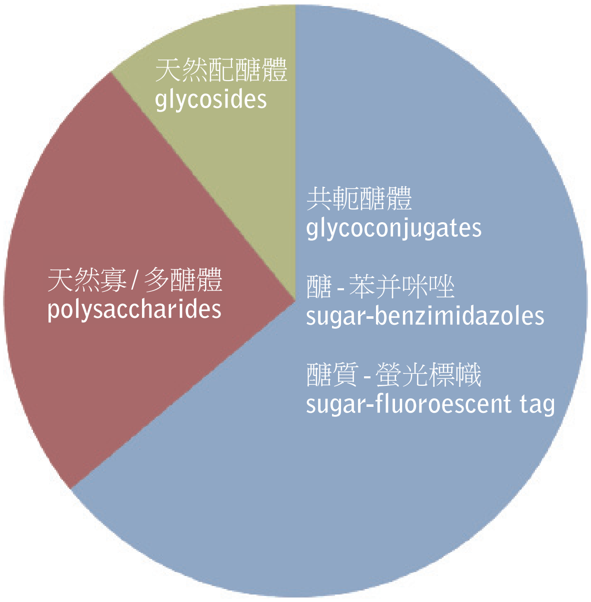
Education and Positions

- Ph.D., Chemistry, National Taiwan University, 1998
- Postdoctoral Fellow, Institute of Biochemistry, Academia Sinica, 1998-2002
- Assistant Professor, Institute of Pharmacognosy, Taipei Medical University, 2002-2003
- Assistant Research Fellow, Genomics Research Center, Academia Sinica, 2003-2013
- Associate Research Specialist, Genomics Research Center, Academia Sinica, 2013-present

Expertise

As an associate research specialist, I am responsible for the glycan isolation and analysis operation on using NMR, GC-MS, LC-MS and MALDI TOF-MS facilities and assist researchers carrying out glycan related researches. I have dedicated myself to provide useful and efficient service, as well as all aspects of advance technical support on carbohydrate disciplines. The duty of my job includes: isolation and analysis of carbohydrates from plant, bacteria and animal cells; supervising the staff members who are studying on glycomics; developing and implementing new automated glycan analyzer; assisting users setting up the experiments for glycan analysis; and providing technical consultation. My expertise is using chemical methods, especially the organic chemistry approach (glycan labeling and permethylation), to obtain structural information of carbohydrates.

主要負責醣類純化及結構分析，利用中心核磁共振儀、氣相層析質譜儀、液相層析質譜儀等來支援研究人員的相關研究。服務內容包括：分離食品、中草藥、植物中的配醣體及多醣體；純化複雜醣鍵結體、如醣蛋白、醣脂質等，並了解其醣基結構；提供使用者技術及實驗規劃之諮詢；協助蒐集相關醣分子之分析圖譜；增加中心藥品庫中醣分子的數量，供快速藥物篩選儀使用；發展或引進自動化醣質分析儀之相關新技術；參與醣質相關研究計畫。



Collecting Glycan Libraries

Hui-Ming Yu 余惠敏

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Education and Positions

- Ph.D. (Biotechnology), Faculty of Science, Chiang Mai University, Thailand, 1999-2004
- Associate Engineer, Institute of Biological Chemistry, Academia Sinica, 1986-2005
- Secretary, The K-T Wong Bioorganic Chwmiarey Foundation, 2000-present
- Manager, Peptide Synthesis Facility, Institute of Biological Chemistry, Academia Sinica, 2001–2005
- Secretary, The Research and Education of Glycosciences Foundation, 2001-present
- Assistant Research Specialist, Genomics Research Center, Academia Sinica, 2006-2012
- Secretary, The Shang-Fa Yang Memorial Foundation, 2008- present
- Associate Research Specialist, Genomics Research Center, Academia Sinica, 2012-present
- Manager, Peptide Synthesis Facility, Genomics Research Center, Academia Sinica, 2012-present
- Secretary, The Taiwan Bio-Development Foundation, 2013-present
- Consultant, The SunTen Phytotech Co., Ltd., 2014-present

Peptide Synthesis Core Facility

This core facility will provide synthetic peptides and fluorescent peptides for biological studies discovered through proteomic research and phage display. It will also provide glycopeptides, phosphor-peptides and peptides with other post-translational modifications for use in structural and functional studies. We will also collaborate with other research groups in GRC to develop methods for synthesizing newly discovered novel peptides and derivatives which can not be prepared with the current routine method, in order to support the research programs in GRC.

Applied Biosystems 433A Peptide Synthesizer

Tsui-Ling Hsu 徐翠玲

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Education and Positions

- Ph.D., Microbiology and Immunology, National Yang-Ming University, Taiwan, 2004
- Postdoctoral Fellow, Genomics Research Center, Academia Sinica, 2005-2007
- Research Associate, Department of Chemistry, The Scripps Research Institute, USA, 2005-2007
- Distinguished Postdoctoral Scholar, Genomics Research Center, Academia Sinica, 2007-2009
- Postdoctoral Fellow, Genomics Research Center, Academia Sinica, 2009-2014
- Assistant Research Specialist, Genomics Research Center, Academia Sinica, 2014-present

Honors

- Award for Excellent Ph.D. Thesis from the Chien-Tien Hsu Cancer Research Foundation at the 7th Symposium on Recent Advances in Cellular and Molecular Biology, 1999
- Travel award from Ministry of Education, 2001
- Award for Excellent Poster from the Chinese Society of Cell and Molecular Biology at the 11th Symposium on Recent Advances in Cellular and Molecular Biology, 2003
- Travel Award for Research Abroad from National Yang-Ming University, 2003
- Yang-Ming Scholarship from Yang-Ming Medical Education Foundation, 2003
- Travel award from Ministry of Education, 2004
- Taiwan Merit Scholarships, 2005-2007
- Outstanding Performance Awards in Genomics Research Center, Academia Sinica, 2013

Expertise

- Employment of exo- and endo-glycosidases to determine site-specific N-linked glycans on the proteins or the glycans derived from biological samples via HPLC and mass spectrometry
- Imaging the trafficking of glycoconjugates in cells, and enrichment of glycoproteins and glycolipids from cell lines or biological samples via sugar tagging and bioorthogonal chemical probes
- Profiling the interaction of pathogen- or cancer-specific glycans with mammalian lectin/innate immune receptors for linking the role of glycans/glycoconjugates to biological systems

- 使用具專一性的切醣酵素作輔助，在高效液相層析儀及質譜儀作醣結構分析
- 使用醣探針技術作細胞內醣類影像追蹤、醣蛋白及醣脂質的分離
- 應用免疫凝集素受體重組蛋白，分析病原體、癌症特有醣類，以瞭解疾病相關醣類在生物體中角色

Chien-Tai Ren 任建台

Assistant Research Specialist

研究助技師

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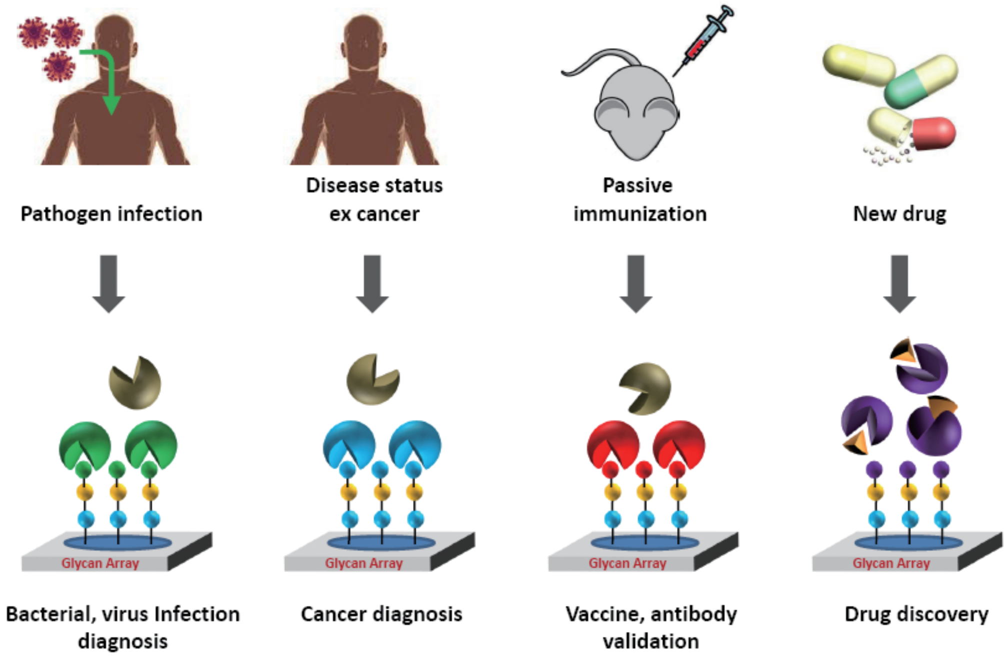
Education and Positions

- Ph.D., Chemistry, Florida State University ,1996
- Postdoctoral Fellow, Florida State University, 1996-1999
- Research Fellow, Sinon Corporation,1999-2000
- Postdoctoral Fellow, Institute of Biological Chemistry, Academia Sinica, 2000-2006
- Assistant Research Specialist, Genomics Research Center, Academia Sinica, 2006-present

Expertise

My research work has been concentrated on the synthesis of biologically active oligosaccharides with designed functionalities or modifications. Many of them are related to human infectious disease and cancers including various sialosides and tumor associated carbohydrate antigens (TACA). The major goal is to establish a representative glycan library with sufficient structural complexity and diversity to support GRC glycan array research programs and carbohydrate-based vaccine developments. In addition, I have participated in GRC peptide synthesis core facility for glycopeptides synthesis, as well as glycan sequencing core facility for methodology development in solving the glycan structures found in nature.

主要的研究工作在於合成各種具有生物活性的寡醣分子，這些寡醣分子大多是與人類傳染病和癌症有關，像是含唾液酸的寡醣體以及與腫瘤相關聯之醣抗原。主要的目的是建立一個具有代表性的寡醣分子庫，在分子結構上具有足夠的複雜性與差異性來支援基因體中心在發展醣晶片以及醣分子疫苗的相關研究課題。同時參與胜肽合成核心設施，支援醣胜肽和醣蛋白方面的合成。並參與醣體定序核心設施，協助發展新的分析方法來訂定自然界所發現的醣體分子結構。



JOINT APPOINTMENTS AND VISITING SCHOLARS/EXPERTS

- Joint Appointments
- Visiting Scholars/Experts

Joint Appointments

In addition to its full-time research faculty members, GRC has brought together scientists and technical specialists from other institutions as joint-appointment faculties to work on various interdisciplinary programs related to genomic research.

Yuan Tseh Lee 李遠哲

President Emeritus and Distinguished Research Fellow 卸任院長，特聘研究員
Institute of Atomic and Molecular Sciences, Academia Sinica
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Research Interest: Reaction Dynamics, Photochemistry Processes, Spectroscopy and Structure of Ionic Clusters
*** Nobel Prize in Chemistry (1986)**
*** President of International Council for Science (ICSU), 2011-2014**
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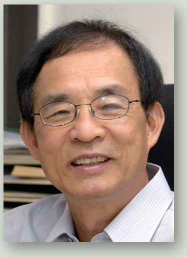

Wen-Hsiung Li 李文雄

Distinguished Research Fellow 特聘研究員
Biodiversity Research Center, Academia Sinica
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*** Balzan Prize in Genetics and Evolution, Italy (2003)**
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Andrew H.-J. Wang 王惠鈞

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Carmay Lin 林小喬

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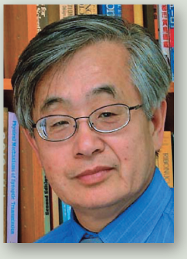

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Distinguished Research Fellow 特聘研究員
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Po-Huang Liang 梁博煌

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Shui-Tein Chen 陳水田

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Yu-Ju Chen 陳玉如

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Mi-Hua Tao 陶秘華

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Shu-Mei Liang 楊淑美

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Agricultural Biotechnology Research Center, Academia Sinica
中央研究院 農業生物科技研究中心
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MAJOR FACILITIES

- Ultra High Throughput Drug Screening Facility
- NMR Facility
- Protein X-ray Crystallography
- Mass Spectrometry Facility
- Peptide Synthesis Facility
- Affymetrix Microarray
- DNA Sequencing Facility
- Glycan Profiling/Sequencing Facility
- Animal Facility
- Biosafety Level 3 Laboratory

Ultra High Throughput Drug Screening Facility

Responsible Persons: Ying-Ta Wu, Ting-Jen Cheng, Shi-Shan Mao

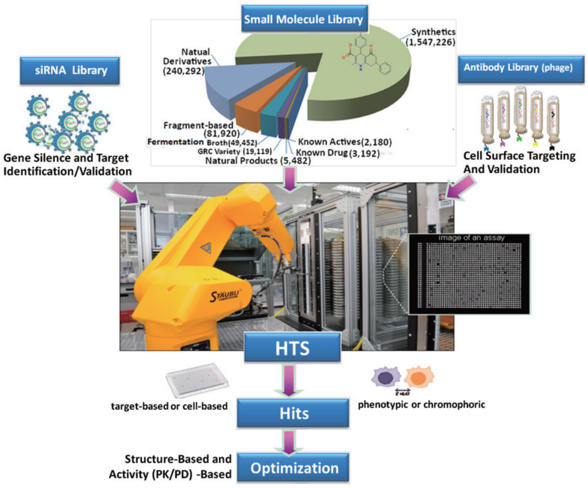
Advanced in miniaturization and automation as well as furnished with extensive compound collections, screening one million molecules in a day has become feasible at the Genomics Research Center, Academia Sinica (GRC). The ultra High-Throughput Screening (uHTS) facility established in the GRC is the first of its kind in Asia. The GRC uHTS is also supported by the National Research Programs for Biopharmaceuticals (NRPB) as the “ChemBank and High Throughput Screening (CB & HTS) Resource Center (SB-1) of NRPB since 2011. The mission of the Resource Center is to provide high-throughput screening services by using GRC’s two-million compound library to help the investigators to rapidly identify bioactive compounds for target mechanism study and therapeutics discovery.

The GRC’s uHTS systems are composed of a screening system and a hit-picking system. Both systems are equipped with 6-axis robot arms for dispatching automatic process to provide unsurpassed screening capacity. The screening system integrates with two dispensers for handling various dispensing/washing modes (0.25uL~10uL), one transfer pintool with precision pins (50nL slot) for transferring compounds in 1536-well micro-titer-plates, and one micro-plate imager with various detection methods for reading assay results. The hit-picking system receives hit list from the screening system and collect hit compounds from the compound library. The resulted hit-compound plates are good for reconfirmation assays and/or other follow-up validations.

To this end, the GRC has collected about 2 million compounds in the library (GRC2M). The majority of these compounds are purified synthetic chemicals. The GRC2M library also contains known drug, biologically active small molecules, natural products and their chemically modified derivatives, herbal, microbial metabolic molecule.

Besides screening the small molecular library, the uHTS system can assist small interfering RNA (siRNA) technology in gene silencing to accelerate the identification of corresponding target genes and the confirmation of specific functional mechanisms. Furthermore, combining with the gene shuffling and phage display techniques, the uHTS system can be used in screening human antibodies produced from single B cells to obtain real human monoclonal antibodies and to speed up the resolution and confirmation of more biological cell surface biomolecules.

The GRC’s uHTS system is operated by a group of experienced staff in developing and automating biological assays as well as conducting biochemical and cell-based screens. In addition, this uHTS facility has medicinal chemists and cheminformatics talents to add values to HTS screening services. The uHTS facility is one important platform at the initial stage of translation research for multi-disciplinary collaboration, linking chemists and biologists to explore disease targets and identify potential interesting compounds for target mechanism studies and drug discovery. It is expected the uHTS setup can benefit the development of biotechnology and pharmaceutical.



NMR Facility

Responsible Person: Chi-Fon Chang

NMR Facility is located on the first floor of Genomics Research Center. The facility maintains two 600MHz Bruker NMR spectrometers. The AV600_R spectrometer is a two-channel system equipped with a 5mm DCI Dual cryoprobe (high sensitivity 1H/13C observation includes cooled preamplifiers for 1H/13C/2H with Z-gradient). A SampleXpress, which hold up to 60 samples, has been installed for medium-throughput automation in NMR routine applications. AV600_R is also connected to a LC system which consists of an Agilent Quaternary Chromatography System and Bruker LC-NMR accessory including on-flow, stop-flow, column switch, extended loop sampling, and solid phase extraction options. A CryoFit accessory with 30ul flow cell is available for LC-NMR application. The AV600_L spectrometer is a three-channel system equipped with a 5mm TCI cryoprobe (1H/13C/15N triple resonance probe head with cooled preamplifiers for 1H/13C/2H with Z-gradient) which could be used for biomolecular NMR application. A SampleXpress Lite , which hold up to 16 samples, has been installed on AV600_L. A regular 5mm BBO-Z probe which is tunable over the frequency range between 31P and 15N (with Z-gradient and automated tuning/matching) is also available in the facility.

Protein X-ray Crystallography

Responsible Investigator: Che Alex Ma

The X-ray diffraction system includes the MicroMax007HF microfocus rotating anode generator with 70x70 micron anode focal spot, the Confocal VariMax optics and two of the R-axis IV^{++} image plate detectors. The MicroMax007HF provides four times the flux as a standard rotating anode generator, for samples of less than 300 microns, allowing to work with weakly diffracting samples or to use shorter exposures during standard data collections. The Confocal VariMax optical system provides an intense monochromatic beam that may be adjusted for flux or resolution to optimize the experimental conditions. The R-axis IV^{++} provides good sensitivity, wide dynamic range, large aperture and fast readout to give data of high quality. The X-stream 2000 low temperature system provides a continuous supply of nitrogen without needing a house source of liquid nitrogen. Each component of this system is fully integrated to maximize its performance for protein crystallography.

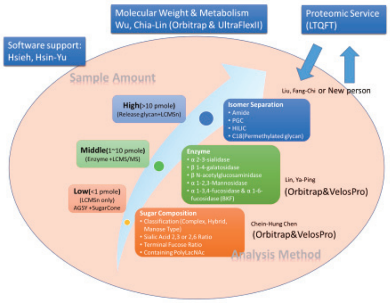
Mass Spectrometry Facility

Responsible Person: Jung-Lee Lin

This facility is core resource which offers state-of-the-art high performance liquid chromatography and tandem mass spectrometric instruments and technical experts for small molecules analysis, proteomics and glycomics analysis.

The major in missions are routine analysis services and developing new methodology for structural analysis of released glycans and glycoproteins in detail based on enzymatic degradation coupled with tandem mass spectrometry. Mass spectrometers in GRC mass facility are as follows.

1. A hybrid fourier transform-mass spectrometer (FT-MS), linear quadruple ion trap (LTQ)-FT Ultra™, which combines fast mass analysis capability of LTQ with ultra high mass accuracy and ultra high mass resolution of 7.4 Tesla superconducting magnet FT-MS. The mass spectrometer provides sensitive and comprehensive proteomic analysis with online nano-liquid chromatography. In additional to conventional collision induced dissociation (CID) at LTQ, extra dissociation capabilities aiming for post-translation modifications (PTM) characterization could be realized by electron capture dissociation (ECD) and infrared multi-photon dissociation (IRMPD) at FT-ICR (Ion Cyclotron Resonance) cell.
2. A hybrid FT-MS, LTQ Orbitrap XL™, is based on the fast and highly sensitive LTQ and the Orbitrap technology, which features a higher energy collision dissociation (HCD) for ultimate flexibility in fragmentation for advanced proteomics research and molecular structural education. This mass spectrometer can be enhanced with the powerful electron transfer dissociation (ETD) and FAIMS capabilities.
3. A Linear quadrupole ion trap mass spectrometer, LTQ XLTM, interfacing online LC, atmospheric matrix-assisted laser desorption/ionization (AP-MALDI) and micro scale chip-based nano electrospray ionization (Triversa NanomateTM) can provide high order tandem mass analysis of phosphor- and glyco-proteomes with the aid of CID and ETD.
4. A MALDI-TOF/TOF mass spectrometer, UltraFlex IITM, provides fast sequence determination of peptide and oligosaccharide. The Ultraflex II consists of two Time-of-Flight (TOF) channels. The first separates the ions generated by laser beam on the basis of their molecular weights giving a mass fingerprint. The second TOF resolves the fragmented species generated by a collision chamber, which is present between the two TOFs.
5. An ESI-TOF mass spectrometer, BioTOF III, is robust for applications that require high resolving power and accurate mass measurement in proteomics, drug discovery, metabolomics, or organic chemistry. Its flexibility and wide mass range make it also ideal for the study of intact proteins or non-covalently bound complexes such as drug-protein, protein-protein, and protein-ligand interactions. With a resolution of > 20,000 for a single pass mode and mass accuracy better than 4 ppm, the BioTOF III is the highest performance ESI-TOF commercially available.
6. A GC-MS (Polaris Q) provides routine chemical identity verification with NIST chemical library for volatile chemicals.



Peptide Synthesis Facility

Responsible Person: Hui-Ming Yu

This core facility will provide synthetic peptides and fluorescent peptides for biological studies discovered through proteomic research and phage display. It will also provide glycopeptides, phosphor-peptides and peptides with other post-translational modifications for use in structural and functional studies. We will also collaborate with other research groups in GRC to develop methods for synthesizing newly discovered novel peptides and derivatives which could not be prepared with the current routine method, in order to support the research programs in GRC.

▲ Applied Biosystems 433A Peptide Synthesizer

Affymetrix® Microarray

Responsible Person: Tzu-Ning Ho

The microarray facility provides two types of platforms for gene analysis: gene expression and whole-genome single nucleotide polymorphism (SNP) genotyping analysis. For gene expression analysis, our platform provides target preparation, hybridization, wash/stain and image scanning for Affymetrix GeneChip. Researchers can use this microarray technology to examine differences of gene expressions in various model organisms including human, mouse, rat and etc. For a whole-genome genotyping analysis, we utilize the Affymetrix oligonucleotide array to screen SNP at genome-wide manner. It could provide the information about the common and rare SNPs, copy number variants, and other genetic variations that can contribute to diseases. The application of genotyping technique includes association study, linkage study, population genetics, chromosomal abnormality, and cancer genomics.

▲ GeneChip® Fluidics Station 450

▲ GeneChip® Hybridization Oven

▲ GeneChip® Scanner 3000 7G & AutoLoader

DNA Sequencing Facility

Responsible Person: Kuo Ping Chiu

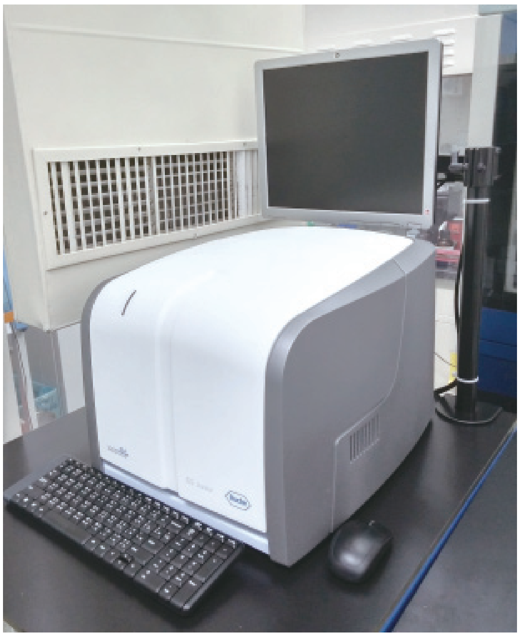
The core facility now offers Roche 454 GS Junior and Illumina MiSeq sequencing services primarily to the research requirements of the GRC investigators.

Illumina MiSeq

The MiSeq desktop sequencer allows you to access more focused applications such as targeted gene sequencing, metagenomics, small genome sequencing, targeted gene expression, amplicon sequencing, and HLA typing. New MiSeq reagents enable up to 15 Gb of output with 25 M sequencing reads and 2x300 bp read length.

Roche 454 GS Junior

The GS Junior System brings the power of 454 Sequencing Systems directly to the laboratory benchtop. Get comprehensive genome coverage with long 400 bp sequencing reads and quickly proceed from DNA to discovery with fast sequencing runs and straightforward data analysis on the attendant computer.



Applications (genome-wide)

1. Genome assembly
2. Transcriptome analysis
3. Mapping of transcription factor bindingsites
4. Mapping of histone modification sites
5. DNA methylation
6. Micro-RNA
7. Software development

Glycan Profiling/Sequencing Facility

Responsible Persons:

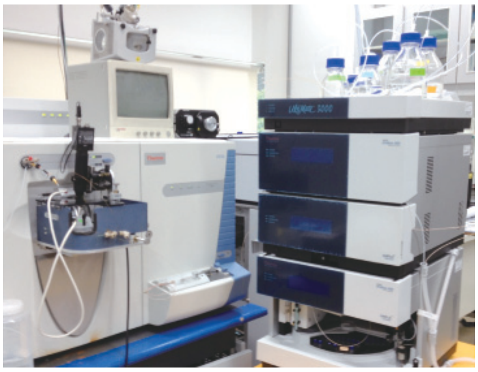
Wen-Bin Yang, Tsui-Ling Hsu, Jung-Lee Lin and Chein-Hung Chen

Glycosylation is involved in all kinds of biological events. The expression and dynamics of glycans can be observed in different physiological processes and pathological status. It is therefore of importance to have systematic investigation of glycosylation, which can lead to the discovery of glycan targets for diagnostic and therapeutic purposes.

The Glycan Profiling/Sequencing Facility in GRC has been established to fulfill the increasing needs of acquiring the glycan information from glycoproteins and glycolipids, including site-specific glycoform profiling of glycoproteins, glycolipid profiling, glycopeptide sequencing, compositional analysis of glycans from biological specimens and nature products, and glycan linkage study, to support glycobiology research.

The Glycan Profiling/Sequencing Facility is equipped with High-Performance Anion-Exchange Chromatography-Pulsed Amperometric Detection (HPAEC-PAD) for sugar compositional analysis, capillary electrophoresis (CE) and HPLC to resolve complex glycans for structural analysis, and state-of-the-art mass spectrometry (MS) facility for delineating glycan structures in detail. Technical platforms encompassing labeling the glycans released from glycoproteins, glyco-enzyme-assisted HPLC and MS for glycan analysis, especially for the distinction of glycan isomers, and permethylation of released glycans for linkage study of glycan structures, are implemented to facilitate sample preparation for glycan analysis.

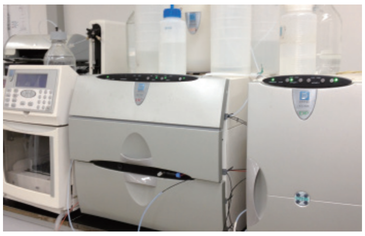
With the integrated technology platforms, we hope to support researchers tackling important biology questions covering glycobiology research and biomarker/drug discovery.



▲ LC-MS^n (LTQ-Orbitrap XL w/ ETD)

▲ MALDI-TOF/TOF MS (UltraFlex II)

▲ GC MS (Polaris Q)



▲ HPAEC-PAD

▲ CE

Animal Facility

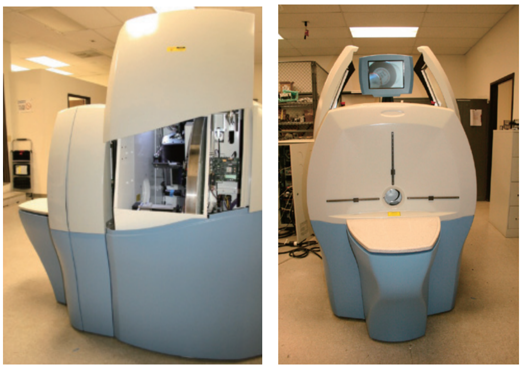
Responsible Person: Michael Hsiao

The Animal Facility in GRC has Specific Pathogen Free (SPF) and P1 animal labs. The fully equipped SPF animal labs contain 5 rooms that are capable of hosting up to 670 cages (3,350 mice) for animal breeding. In addition, two procedure rooms are set up. One room is used for surgical procedures for removing tissues and withdrawing blood for further genotyping and phenotyping analysis of the SPF animals. The other room is used for optical based luciferase and/or fluorescence-based imaging to observe the specific transgene or knockout phenotypes of the animals. This room is also equipped with an X-ray irradiator for lethal or sub-lethal irradiation of the animal followed by transplantation of stem cells or cancer stem cells as well as evaluating radiosensitivity of tumor cells in vivo. Currently, more than 10 strains of transgenic or knock-out mice in the facility. They will be used for breeding and later be used to as murine models for many human tumor models such as breast, or colon cancers. In additional, other immunodeficient mice will also be used to serve as sources for many human xenograft models.

An integrated imaging platform has been installed in the Animal Facility to monitor disease processes and understand the effects of new drug treatments effectively, over time with repeat measurements for the same animal. The Triumph™ Trimodality system is a fully integrated SPECT/PET/CT hardware and software platform optimized for small animals in pre-clinical and biomedical research applications. The functional imaging of SPECT and PET are fused with anatomical imaging provided by X-ray Computed Tomography. This way, users can precisely identify the location of an abnormality related to the surrounding anatomical structure. The main applications of this machine are for disease detection, drug tracking, micro-dosing, pharmacokinetics, biomarker development. It's a useful tool for pre-clinical imaging and functional test.

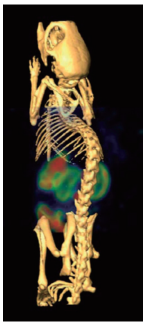
▲ IVC and Hood

▲ X-ray Biological Irradiator

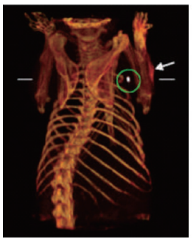


▲ The Triumph™ Trimodality System

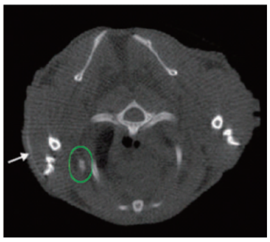
▲ IVIS® Kinetic



▲ SPECT/ CT image



▲ PET/CT image



▲ CT image

Biosafety Level 3 Laboratory

Responsible Person: Jia-Tsrong Jan

The Biosafety Level 3 (BSL-3) laboratory in GRC is set for providing supportive experiment practices mainly for institutional researches against naturally occurring infectious microorganisms of high-risk to humans that require special containment devices, appropriate personal protective equipment, and rigorous regulations. The GRC BSL-3 laboratory is well organized with experienced team members and is equipped with appropriate safety containments for both in vitro cell-based assays and in vivo small animal experiments.

A BSL-3 laboratory is constructed specifically for research or clinical work with infectious microorganisms that may cause serious or potentially lethal disease as a result of exposure especially through inhalation route. The major infectious microorganisms performed in such laboratory are classified as Risk Group 3 that has high individual risk but lower community risk than those of RG-4 in a BSL-4 laboratory. Examples of RG-3 members attracting more attention in Taiwan include: SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), avian influenza virus (H5N1, H7N9, H6N1, and H5N2), human influenza virus (swine flu virus, 2009), HIV, hantaviruses, poliovirus, West Nile virus, monkeypox virus, Mycobacterium tuberculosis, Yersinia pestis, and prions.

GRC BSL-3 laboratory has the certificate from Taiwan's Centers for Disease Control (DCD) to work on RG-3 microorganisms-related researches. Currently, the laboratory has a class II-B2 biosafety cabinet (BSC), an individual ventilation cage (IVC) system, a class III small animal isolator, and two self-designed ferret-specific negative-pressure isolators. With all these containment equipments and well–trained staffs, GRC BSL-3 laboratory is able to perform service for drug screening and vaccine efficacy evaluation against RG-3 microorganisms, and related pathology studies in both cell-based assays and animal experiments using different small animal models including ferret which has been long recognized as of the best animal model for SARS and flu studies.

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