LANDSCAPE

NTU RESEARCH AND DEVELOPMENT

Issue 1 July 2016
Inaugural Edition

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國立臺灣大學
National Taiwan University

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Editorial Notes

A recent report released on April 15, 2016 by Taiwan's Health Promotion Administration (HPA) indicated that 99,143 people were diagnosed with cancer in 2013, an increase of 2,449 people from the previous year. Claiming 46,094 lives or 28.3 percent of the 162,911 total deaths in 2014, cancer has remained the top cause of death in Taiwan for 33 years, according to Taiwan's Ministry of Health and Welfare on June 17, 2015. Physicians and researchers of National Taiwan University have been dedicated to reversing the formidable trend over the past years while establishing comprehensive support network from prevention, early diagnosis, and treatment to palliative care.

This opening issue of Transforming Cancer Research features the effects of Cdc13 phosphorylation on how cancer cells replicate by synthesizing telomeres, as investigated by SHU-CHUN TENG ET AL. FANG-JEN LEE, CHIA-WEI HSU ET AL. identified a novel guanine nucleotide exchange factor (GEF) named Snf1p, which is responsible for Arf3p activation in response to glucose depletion. In energy-depleted environments, cells are stimulated to migrate toward nutritional or carbonic sources and may become invasive. Understanding the regulatory pathway underlying the mechanism of Arf3p- and Snf1p-mediated invasive growth could enable new drug development. CHIH-PENG LIN, WEI-ZEN SUN AND WEN-MEI FU investigated the intraspinal cytokine and chemokine profiles of opioid-tolerant cancer patients and determined whether up-regulated chemokines could modify opioid tolerance in rats. This discovery could inspire the development of new drugs to inhibit the effects of CXCL1, which could stabilize the effects of opioid painkillers.

EARLY DIAGNOSIS of lung adenocarcinoma is difficult because there are no obvious symptoms and no history of smoking. Collaborative work of teams including GEE-CHEN CHANG AND MINE revealed that the YAP1 R331W mutation plays an important role in lung adenocarcinoma and has high penetrance.

Epidemiological studies have linked type 2 diabetes to pancreatic adenocarcinoma, but the link between blood glucose and pancreatic cancer remains controversial. WEI-CHIH LIAO, YU-KANG TU AND KUO-LIONG CHIEN's research demonstrated that the incidence rate of pancreatic adenocarcinoma increases linearly with increasing fasting blood glucose in both prediabetes and diabetes. Since prediabetes precedes type 2 diabetes by years and can be improved or reversed by lifestyle changes, pre-diabetes may provide an important window of opportunity for pancreatic cancer prevention.

Most primary liver cancers are classified as hepatocellular carcinoma (HCC). HCC is the second leading cause of cancer-related deaths worldwide and is responsible for approximately 600,000 deaths annually. Treatments for HCC include surgical resection, thermal, radiofrequency or chemical ablation, and embolization. Median survival time in HCC patients is short, though longer in patients treated with surgery (52 months) compared to embolization or ablation (16 and 11 months, respectively). WEI-CHU CHIE, MENG-QIAN LI ET AL. indicated that patients tended to have a higher risk for quality-of-life deterioration when they were treated with radiofrequency ablation compared to embolization or surgery, which is valuable information for patients when they are choosing which treatment to receive.

Also highlighted in this issue includes: CHUAN-CHOU SHEN ET AL. utilized high-precision radiometric uranium-thorium techniques to date three selected sacred Leluh tombs. The team discovered that these coral pyramidal tombs in Micronesia were created in the 14th century, approximately 600-700 years ago. WEI-PING LIN's most recent work, Materializing Magic Power: Chinese Popular Religion in Villages and Cities, is an important contribution to the anthropology of religion. In this book, Lin discusses how statues are employed to tie gods to a particular village and how personal relationships are constructed between gods and villagers through those statues.

More research breakthroughs are to be found in this biannual publication demonstrating how our researchers improve existing approaches and develop new ways to address a broad spectrum of challenges.

Pan-Chyr Yang, M.D., Ph.D.
President
National Taiwan University

Cover Story

National Taiwan University Hospital (NTUH), originally established as Taiwan Hospital, was founded in 1895. It was initially located at Dadaocheng in Taipei, and was relocated to the present site (also known as “the West Campus”) in 1898. It was the largest and the most modern hospital in Southeast Asia when it was completed in 1921. Two years after the establishment of NTUH, the Japanese government established National Taiwan University College of Medicine (NTUCM), formerly called Taipei Hospital Medical Training Institute. Later in 1899, Taiwan Sōtokufu Medical School was established, and was renamed Taipei Medical Professional School in 1927, and subsequently incorporated into the Taipei Imperial University in 1936 to offer professional medical education and cultivate medical doctors. After the retrocession of Taiwan in 1945, the Taiwanese Government took over, and Taipei Imperial University was renamed National Taiwan University (NTU). To date, NTU has 11 colleges, with 54 departments and 103 graduate institutes, plus four university-level research centers: Population and Gender Studies Center, Center for Condensed Matter Sciences, Center for Biotechnology, and Bio-diversity Research Center.

The following schools of allied health sciences were established within the College of Medicine (28 departments): Pharmacy, Dentistry, Nursing, Clinical Laboratory Sciences and Medical Biotechnology, Physical Therapy, and Occupational Therapy. In addition to these 7 schools, 23 graduate institutes and 4 research centers as well as the Laboratory Animal Center (1990) were established to facilitate the development of advanced study in medical sciences and the promotion of research in medical fields. The 4 research centers are the Center for Optoelectronic Biomedicine (1987), the Cancer Research Center (2000), the Drug Research Center (2001) and the NTU Center of Genomic Medicine (2003).

Together with the Department of Oncology of NTUH established in 1993, the Cancer Research Center Program was the first to set up in domestic university hospitals. We combine the expertise of multi-department specialists for the diagnosis and treatment of cancer patients and provide an efficient, high-quality humane medical treatment plan set. We set up special interdisciplinary clinics for lung cancer and breast cancer during the same period, inviting physicians, surgeons, radio-oncologists, and pathologists to make the diagnosis and treatment plan for cancer patients and provide multiple strategies for cancer treatment. In 2011, the center serviced 108,651 outpatients and 5,027 hospitalized patients, provided 44,403 outpatient chemotherapy and 58,890 radiation treatment. On December 19, 2008, Yonglin Healthcare Foundation (founded by Terry Gou, chairman of Foxconn Technology Group) and NTU signed a donation agreement, committing to build a world-class cancer center which will be the first of its kind in the Chinese-speaking world. With the mutual efforts of NTU, NTUCM, and NTUH, National Taiwan University Cancer Center (NTUCC) is expected to open in 2018. We welcome experts from all fields to join our team.

Contents

The mechanism stopping DNA replication inspires cancer research

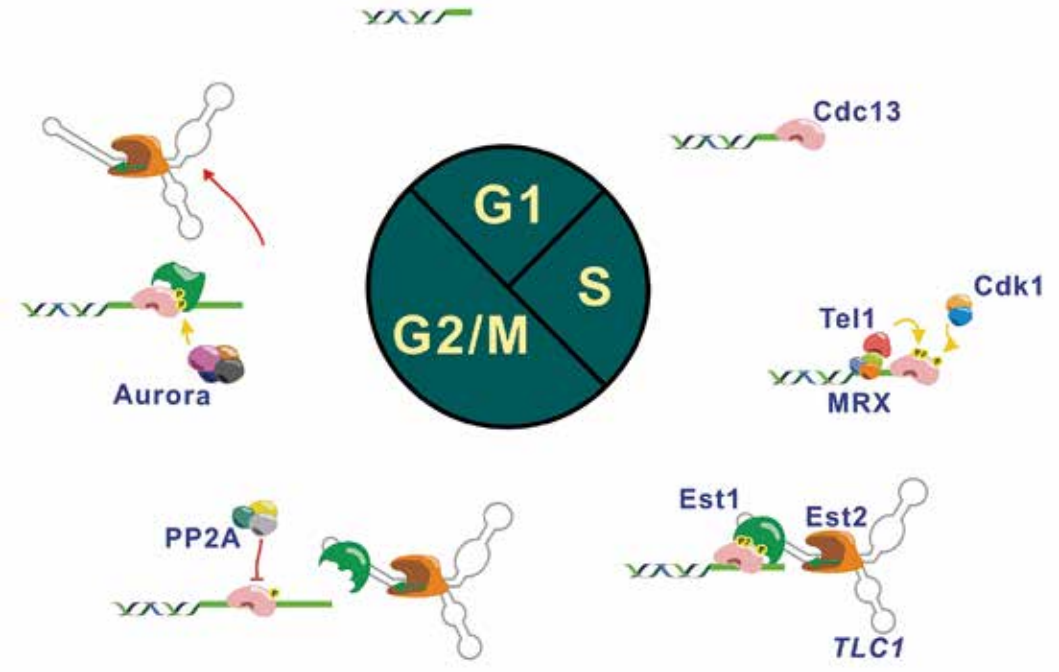
NTU discovers how cell stabilizes its division through terminating telomere replication, inspires cancer research

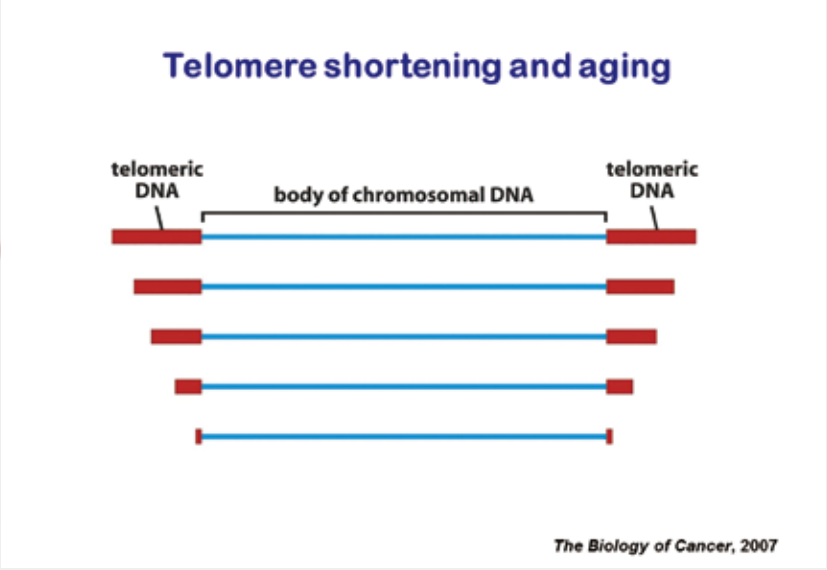
The National Taiwan University research team, which is led by Prof. Shu-Chun Teng from the Department of Microbiology, College of Medicine, has discovered a mechanism related to DNA replication and cellular stability. This discovery is very likely to have crucial implications for cancer research and treatment because understanding this mechanism might allow scientists to prevent harmful chromosome rearrangements and genomic instability in cancer. This research was accepted and published by the reputable journal Nature Communications in 2014.

Teng's team specializes in studying the function of the 'telomere,' a region of sequences protecting the ends of chromosomes and stabilizing cells. How cells synthesize telomeres has long been a puzzle for biologists. Nevertheless, the answer to this question might help biologists understand why most cells remain unreplicated while cancer cells actively execute cell division. From previous studies in the field, it is known that three major regulatory molecules, CDKs, Aurora and Polo-like kinases, coordinate cell division. During this coordination, Cdc13, one of the CDK's substrates, plays a decisive role in telomere protection in live organisms. In addition, recent reports have suggested that 'phosphorylation,' a metabolic process in the cell cycle, may trigger the action of telomeres. However, this suggestion lacks empirical justification. Therefore, Teng's team aimed at addressing this research gap by investigating the effects of Cdc13 phosphorylation.

Through an experiment on yeast, Teng's team discovered

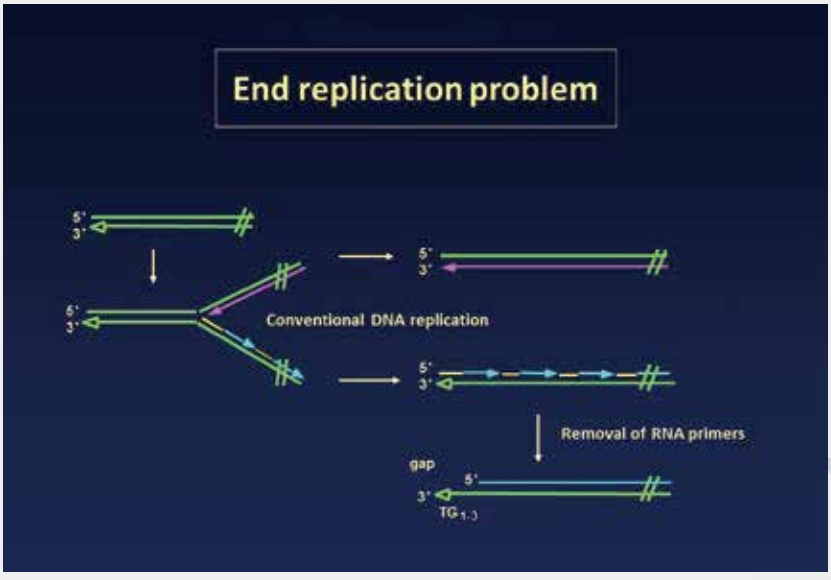
Start and end of the chromosome end replication





the importance of telomeres in stabilizing cells during the DNA replication process. In their experiment, they inactivated two regulatory molecules, Cdc13 and Aurora kinase, and found that this inactivation causes telomere elongation and a prolonged cell division phase. In addition, they also found a protein, 'protein phosphatase 2A (PP2A),' that functions in the de-phosphorylation process of Cdc13 substrates. This protein promotes telomerase release in the telomeres while opposing Cdc13's activation. In other words, in an independent but complementary manner, phosphatase and Aurora kinase use distinct mechanisms to release telomerase from telomeres. Thus, Teng's team has solved a puzzle for biologists around the world and has revealed the mechanism of how telomeres function in the cell cycle and stabilize cells.

Interestingly, cells use multiple pathways to release telomerase. Teng's team has discovered that not only the initiation but also the termination of telomerase recruitment plays important roles in telomere maintenance and cell cycle progression. Teng's team further predicts that in a single cell, PP2A phosphatase might facilitate telomerase release from some telomeres, whereas Aurora kinase might promote telomerase release from other telomeres. Their prediction also hints at directions for future research.



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Invasion

Unraveling the mechanism underlying invasive yeast growth

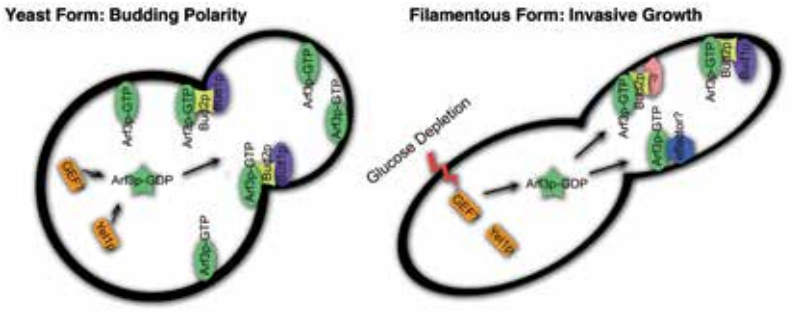
In energy-depleted environments, cells are stimulated to migrate toward nutritional or carbonic sources and, in some cases, may even become invasive.

Why is this so?

Many fungi will switch to filamentous growth to search for nutrients in energy-depleted environments. Filamentous growth is considered invasive and is associated with Arf3p activation in yeast, which is the homolog of mammalian Arf6.

ADP-ribosylation factors (Arfs) are small GTP-binding proteins that can hydrolyze GTP and have critical roles in vesicle transport and actin reorganization. Six Arf isoforms have been identified in mammalian cells, which can be divided into three classes. Class I (Arf1-3) and class II (Arf4-5) Arfs primarily regulate vesicular trafficking between the Golgi and endoplasmic reticulum. Class III Arfs (Arf6) have been implicated in endocytosis, plasma membrane protein recycling and cytoskeleton remodeling. Arf6 also plays a role in cell adhesion, migration, wound healing, membrane ruffling and metastasis.

Similar to other small GTP-binding proteins, the activation of Arf is strictly regulated by guanine nucleotide-exchange factors (GEFs), which facilitate the dissociation of GDP and its replacement with GTP. All Arf GEFs are characterized by a central catalytic domain known as the sec7 domain.



In addition to invasive growth, Arf3p is also involved in polarity development in yeast. During this process, Arf3p activation is mediated by Yel1p, which acts as the GEF; however, further studies have revealed that Yel1p is not responsible for the activation of Arf3p upon glucose deprivation.

Therefore, the key GEF involved in invasive growth was uncertain.

In July 2015, Professor Lee and Doctor Hsu published their study in Nature Communications on the mechanism of Arf3p activation in energy-depleted environments.

In this study, the authors identified a novel GEF named Snf1p. Snf1p is the yeast homolog of mammalian AMP-activated protein kinase (AMPK), which is responsible for Arf3p activation in response to glucose depletion. Snf1p is a key metabolic regulator of energy homeostasis and is involved in yeast invasive growth. Snf1p directly binds to and activates Arf3p through the C-terminal regulatory domain. Unlike other Arf GEFs, Snf1p lacks the sec7 domain and acts independent of N-terminal Snf1p kinase activity.

In conclusion, Arf3p and Snf1p, the homologs of mammalian Arf6 and AMPK, respectively, are associated with yeast invasive growth in glucose-depleted environments. Recent studies have also shown that Arf6 and AMPK may be related to cell migration and invasion in cancer. Understanding the regulatory pathway underlying the mechanism of Arf3p- and Snf1p-mediated invasive growth may facilitate new drug development in the future.

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New discovery will inspire treatments for severe cancer pain

NTU scientists determined the underlying cause of the decrease in function of certain cancer painkillers, which will inspire the development of novel drugs

In clinical practice, a patient's tolerance for opioid painkillers is a consistently difficult issue to manage. This issue is particularly relevant for patients with serious cancer because the long-term use of opioids to alleviate their severe pain inevitably leads to decreased efficacy of the medication. To improve the quality of clinical treatment for these patients and to investigate the physiological reaction to opioid painkillers, a research team led by Dr. Chih-Peng Lin, Prof. Wei-Zen Sun and Prof. Wen-Mei Fu at the National Taiwan University College of Medicine has been studying this topic for more than three years. Their research led to the discovery of a cytokine signaling protein, CXCL1, in cancer patients' central nervous systems and that it influences the effects of opioid painkillers. This discovery could inspire the development of new drugs to inhibit the effects of CXCL1, which could stabilize the effects of opioid painkillers. These results were published in the most reputable anesthesia medical journal, Anesthesiology, in 2015.

First, the research team compared cerebrospinal fluid samples from two groups: opioid-tolerant cancer patients and opioid-naive subjects. They found that the amount of CXCL1 in the cerebrospinal fluid was significantly higher in the opioid-tolerant group. In addition, the CXCL1 level in the cancer patients increased as the opioid dose increased. Second, the research team conducted animal experiments to support their findings. After opioid painkillers were injected into the spines of rats, the spinal fluid levels of CXCL1 increased significantly within 48 hours. Additionally, administering a CXCL1 antibody to the rats, which neutralizes the effects of CXCL1, enhanced the effects of the opioid painkillers in the rats, demonstrating that CXCL1 is an important substance that affects live organisms' tolerance for opioid painkillers.

Dr. Lin and Prof. Sun have dedicated themselves to improving and creating innovations in the treatment of cancer pain for many years. In this study, they were responsible for the clinical care, the collection of cerebrospinal fluid and the data analysis. The pharmacology team was led by Prof. Fu, who specializes in animal research and novel drug development. This crucial study was accomplished through their expertise and teamwork.

Because the CXCL1 signaling pathway may be a novel target for the treatment of opioid tolerance, and because of the potential of this study in inspiring future drug development, it was elected by the American Society of Anesthesiologists (ASA) as the most important scientific discovery in its issue of the journal. This research provides a crucial scientific contribution and great benefit to society. Therefore, the ASA disseminated this study widely throughout both the scientific community and the media. For example, this scientific breakthrough was also published on the Forbes website.

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The genetic mystery behind lung cancer

A YAP1 mutation is a germline risk allele for lung adenocarcinoma

According to statistics from the Ministry of Health and Welfare in Taiwan, lung cancer is the leading cause of death among malignancies. In non-smokers, lung adenocarcinoma is the predominant histologic type. However, early diagnosis of lung adenocarcinoma is difficult because there are no obvious symptoms and no history of smoking.

Because early symptoms of lung adenocarcinoma are vague, genetic factors may be useful for screening.

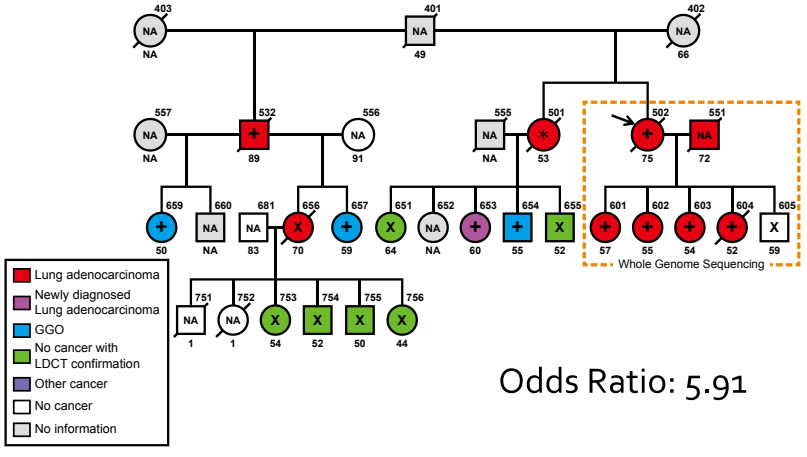
Compared with hereditary factors in many other human neoplastic diseases, the role of hereditary factors in lung cancer is still poorly understood. Genome-wide association studies (GWASs) have identified some common genetic variants, including 15q25, 6p21, and 5p15, that confer susceptibility to lung adenocarcinoma. However, these variants are common alleles, with allelic frequencies higher than 20%. In addition, the penetrance is also low, which means that only a few people with these genetic variants will develop lung adenocarcinoma. Taken together, these genetic variants are of limited clinical utility.

Therefore, it is important to identify potential actionable alleles to identify patients with lung adenocarcinoma.

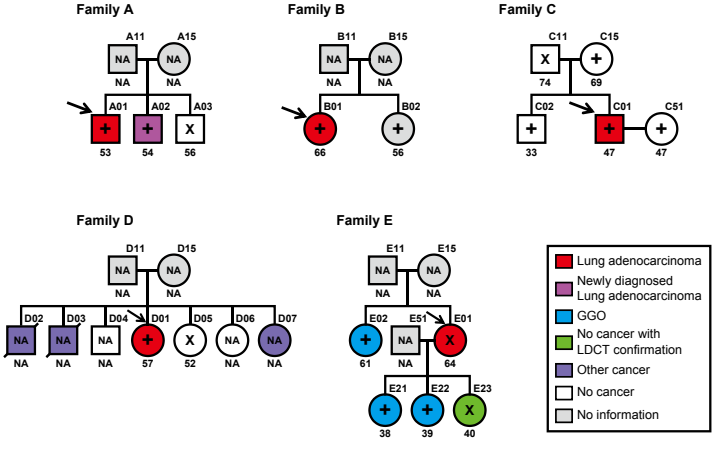
In July 2015, Professor Yang and colleagues published their study in the Journal of Clinical Oncology concerning the identification of genes associated with lung adenocarcinoma using whole-genome sequencing.

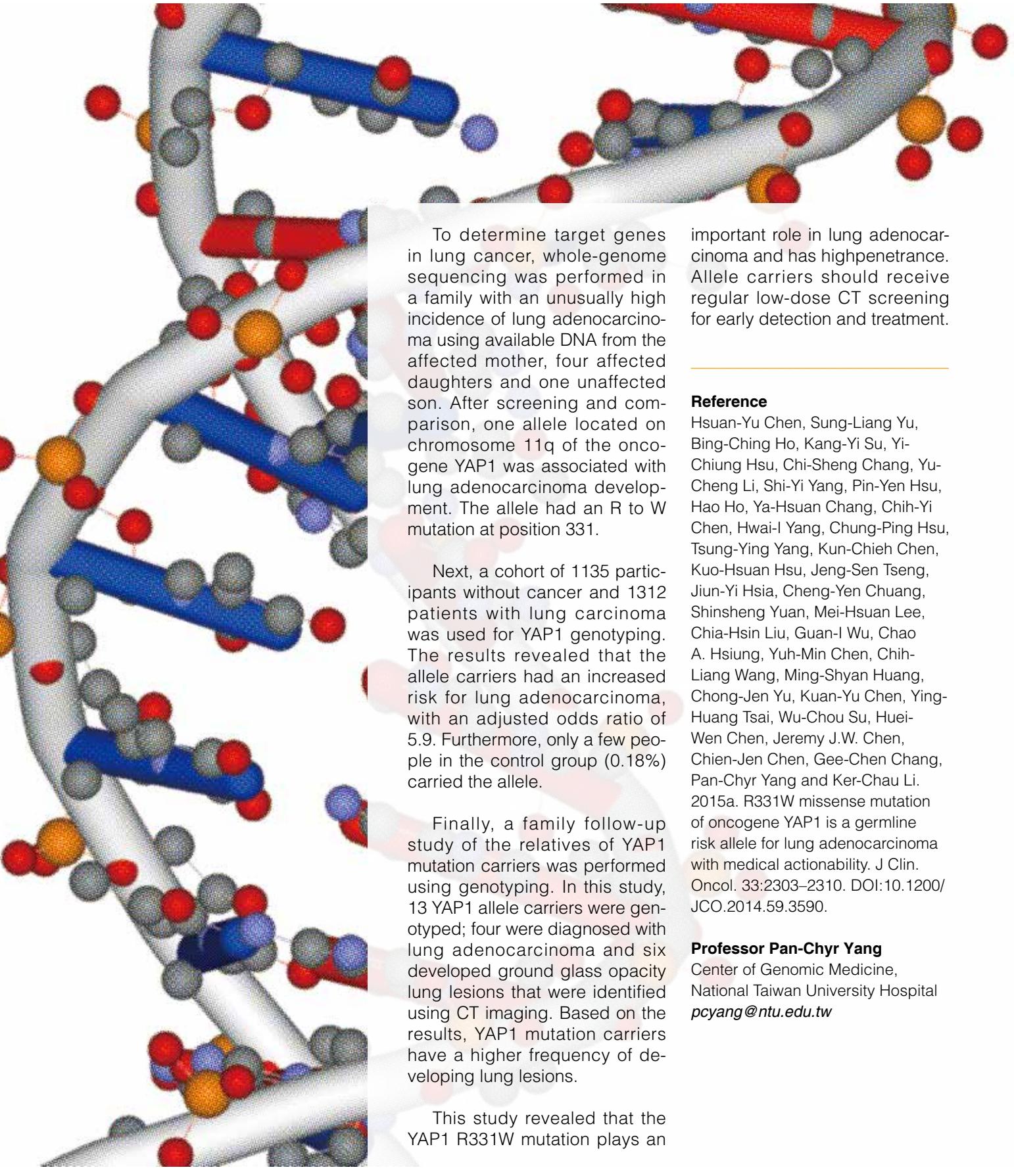
Previously, whole-genome sequencing was a time-consuming process; the Human Genome Project took nearly 13 years to complete. However, technological advances have decreased the processing time of whole-genome sequencing to only 1 week.

YAP1 is a potent oncogene, amplified in various cancers and involved in the Hippo pathway.



Odds Ratio: 5.91





To determine target genes in lung cancer, whole-genome sequencing was performed in a family with an unusually high incidence of lung adenocarcinoma using available DNA from the affected mother, four affected daughters and one unaffected son. After screening and comparison, one allele located on chromosome 11q of the oncogene YAP1 was associated with lung adenocarcinoma development. The allele had an R to W mutation at position 331.

Next, a cohort of 1135 participants without cancer and 1312 patients with lung carcinoma was used for YAP1 genotyping. The results revealed that the allele carriers had an increased risk for lung adenocarcinoma, with an adjusted odds ratio of 5.9. Furthermore, only a few people in the control group (0.18%) carried the allele.

Finally, a family follow-up study of the relatives of YAP1 mutation carriers was performed using genotyping. In this study, 13 YAP1 allele carriers were genotyped; four were diagnosed with lung adenocarcinoma and six developed ground glass opacity lung lesions that were identified using CT imaging. Based on the results, YAP1 mutation carriers have a higher frequency of developing lung lesions.

This study revealed that the YAP1 R331W mutation plays an important role in lung adenocarcinoma and has highpenetrance. Allele carriers should receive regular low-dose CT screening for early detection and treatment.

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Hsuan-Yu Chen, Sung-Liang Yu, Bing-Ching Ho, Kang-Yi Su, Yi-Chiung Hsu, Chi-Sheng Chang, Yu-Cheng Li, Shi-Yi Yang, Pin-Yen Hsu, Hao Ho, Ya-Hsuan Chang, Chih-Yi Chen, Hwai-I Yang, Chung-Ping Hsu, Tsung-Ying Yang, Kun-Chieh Chen, Kuo-Hsuan Hsu, Jeng-Sen Tseng, Jiun-Yi Hsia, Cheng-Yen Chuang, Shinsheng Yuan, Mei-Hsuan Lee, Chia-Hsin Liu, Guan-I Wu, Chao A. Hsiung, Yuh-Min Chen, Chih-Liang Wang, Ming-Shyan Huang, Chong-Jen Yu, Kuan-Yu Chen, Ying-Huang Tsai, Wu-Chou Su, Huei-Wen Chen, Jeremy J.W. Chen, Chien-Jen Chen, Gee-Chen Chang, Pan-Chyr Yang and Ker-Chau Li. 2015a. R331W missense mutation of oncogene YAP1 is a germline risk allele for lung adenocarcinoma with medical actionability. J Clin. Oncol. 33:2303–2310. DOI:10.1200/JCO.2014.59.3590.

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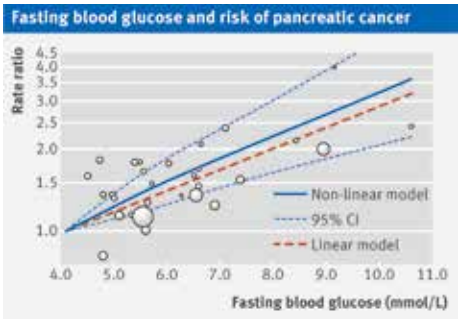
Fasting blood sugar and risk of pancreatic cancer

Elevated fasting blood sugar is associated with an increased risk of pancreatic cancer even in the prediabetic range

The incidence rate of the highly lethal cancer pancreatic adenocarcinoma is increasing. Epidemiological studies have linked type 2 diabetes to pancreatic adenocarcinoma, but the link between blood glucose and pancreatic cancer remains controversial. Dr. Wei-Chih Liao, an attending physician at National Taiwan University (NTU) hospital, has conducted a systematic review and dose-response meta-analysis of the relationship between blood glucose concentration and the risk of pancreatic cancer, which was published in BMJ on January 2, 2015. The analysis demonstrated that the incidence rate of pancreatic adenocarcinoma increases linearly with increasing fasting blood glucose in both prediabetes and diabetes. This study is part of Dr. Liao's PhD work supervised by Associate Professor Yu-Kang Tu and Professor Kuo-Liong Chien, both at the Institute of Epidemiology & Preventive Medicine, College of Public Health.



Nine observational studies with a total of 2,408 pancreatic cancer patients among 2,989,500 subjects were included in this meta-analysis. A random-effects dose-response meta-analysis was conducted to explore potential linear and nonlinear dose-response relationships between blood glucose and the incidence rate of pancreatic cancer.

There was a strong linear relationship between fasting blood glucose and the incidence rate of pancreatic in both pre-diabetes and diabetes, without a significant nonlinear association. The pooled pancreatic cancer rate ratio per 10 mg/dL increase in fasting blood glucose was 1.14 (95% confidence interval: 1.06 to 1.22; P<0.001) across the blood glucose range between 73.9 mg/dL and 191 mg/dL.

Sensitivity analysis excluding blood glucose categories in the range of diabetes yielded similar results (pooled rate ratio per 10 mg/dL increase in fasting blood glucose: 1.15; 95% confidence interval: 1.05 to 1.27; P=0.003), thus strengthening the association between pre-diabetes and pancreatic cancer. No significant heterogeneity or outlying studies were found. The results of gender-specific analyses were consistent with those of the main analyses combining both genders and also revealed a linear dose-response relationship.

In conclusion, every 10 mg/dL increase in fasting blood glucose is associated with an average increase in the incidence rate of pancreatic cancer of 14%. Pre-diabetes is also a risk factor for pancreatic cancer. Because prediabetes precedes type 2 diabetes by years and can be improved or reversed by lifestyle changes, pre-diabetes may provide an important window of opportunity for pancreatic cancer prevention.

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Life after cancer

Changes in quality of life after treatment for hepatocellular carcinoma

Most primary liver cancers are classified as hepatocellular carcinoma (HCC). HCC is the second leading cause of cancer-related deaths worldwide and is responsible for approximately 600,000 deaths annually. The incidence of HCC varies across different regions but is particularly high in East Asia and Sub-Saharan Africa. In addition, the incidence of HCC in males is more than twice that in females. According to statistics from the Ministry of Health and Welfare, HCC was the second leading cause of death among malignancies in Taiwan in 2014.

Following a diagnosis of HCC, treatments include surgical resection, embolization, radiofrequency ablation (RFA), chemical ablation, chemotherapy and targeted therapy. Because the overall prognosis for HCC is poor, the quality of life (QoL) after treatment should also be taken into consideration.

It was not until the 1990s that health-related QoL among cancer patients began to receive attention. Indeed, studies have indicated that sex, age, stage of HCC and liver function are all associated with QoL in HCC patients. Overall, QoL tends to worsen as the TNM stage progresses. When QoL was assessed 24 months after treatment, one study conducted in Italy concluded that RFA was associated with worse QoL compared to hepatic resection but better QoL compared to transarterial chemoembolization or no treatment in HCC patients.

However, no previous studies had investigated the treatment experience in Asian HCC patients. How will these treatments affect QoL in an Asian population?

In May 2015, Professor Chie, from the Department of Public Health, National Taiwan University, and Mengqian Li, from the Department of Biostatistics, University of Nebraska Medical Center, published a study of the effects of different treatments on QoL in Asian HCC patients.

The research team utilized the QLQ-C30 and QLQ-HCC18 questionnaires to compare QoL following embolization, RFA or surgical resection. Adjustments were made for many potential confounding factors, including age, sex, race, employment status, whether the participant was living with family, comorbidity, stage of HCC, liver function and QoL score before treatment. After adjusting for these factors, the results indicated that patients tended to have a higher risk for QoL deterioration when they were treated with RFA compared to embolization or surgery.

This study revealed the changes that occur in QoL after different HCC treatments, which is valuable information for patients when they are choosing which treatment to receive.

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Criegee intermediate

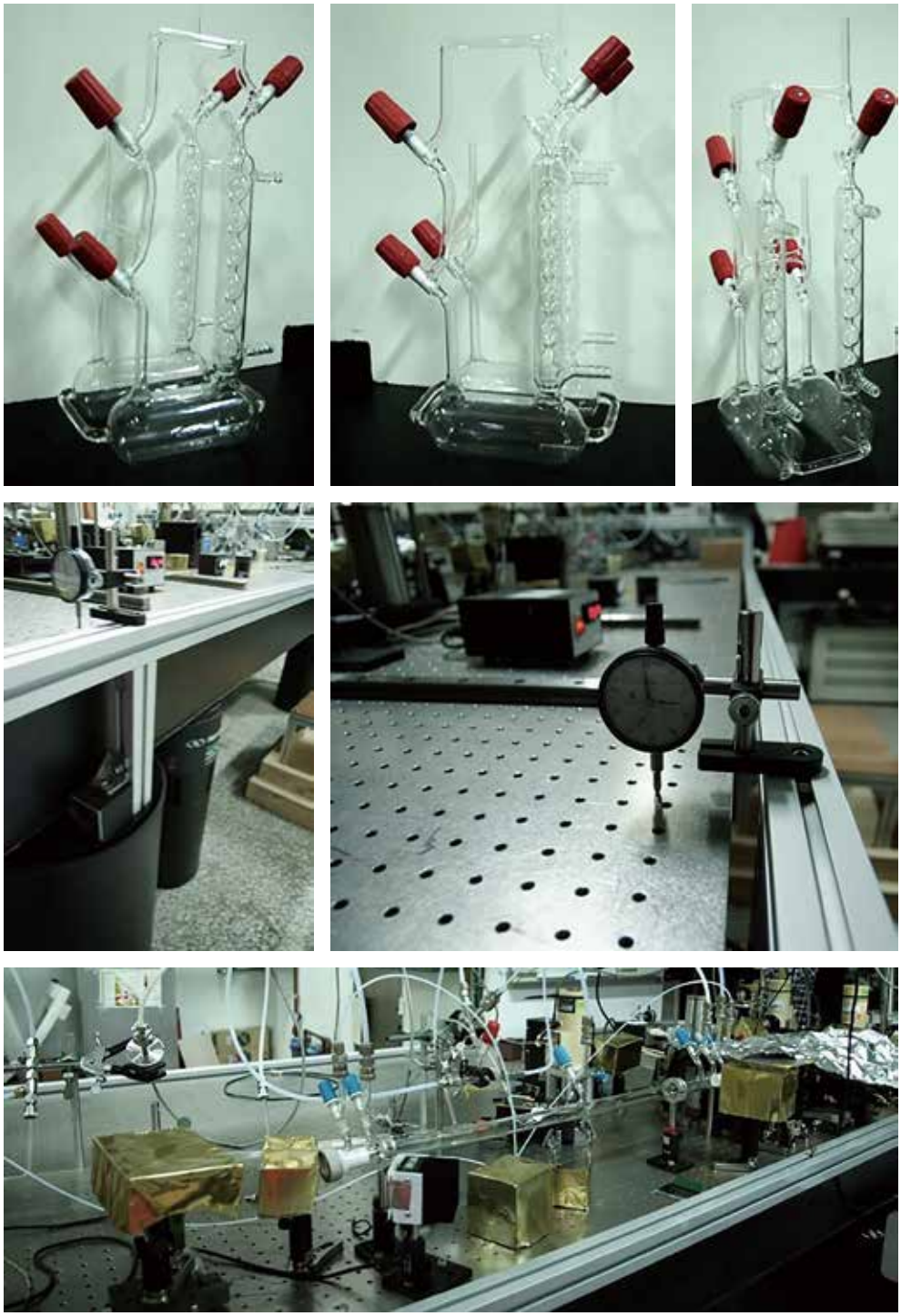
The ghost in the air

The simplest Criegee intermediate can react very rapidly with water vapor, and the reaction kinetics demonstrates a quadratic rate dependence on the concentration of water molecules, which indicates that two water molecules are required to react with one Criegee intermediate. This research result demystified the reaction kinetics between Criegee intermediate and water vapor, and thereupon has calmed academic disputes and caught the attention of international community in atmospheric chemistry. “Our result is different from previous knowledge and views, and I think this should be made known to all.” Prof. Jim Jr-Min Lin said confidently. Prof. Lin’s team has published this research on Science, the issue of January, 2015.

The formation of sulfuric acid in the atmosphere involves oxidation of sulfur dioxide (SO_2) to sulfur trioxide (SO_3). This process has always been an important research project because sulfuric acid, with a very low vapor pressure, is prone to transform into liquid particulates (one of the components of PM 2.5) which heavily affect the atmosphere. However, the reason why sulfur dioxide can be rapidly oxidized into sulfur trioxide still remains unclear. Since the monitored SO_2 oxidation rate is higher than the estimated value in the atmospheric chemistry model, scientists therefore assume the existence of other oxidizing reactions. Some had put forward the possibility that the strong oxidant, Criegee intermediate, played an important role in the SO_2 oxidation process, and an article published in Nature in 2012 discussed this assumption. But Prof. Lin holds the view that these studies had not made one very basic thing clear: whether water vapor reacts with Criegee intermediate. Because the water vapor content in the atmosphere is over a million times those of atmospheric pollutants like SO_2, and if most Criegee intermediates react with water, there cannot be considerable amount of Criegee intermediates to react with sulfur dioxide.

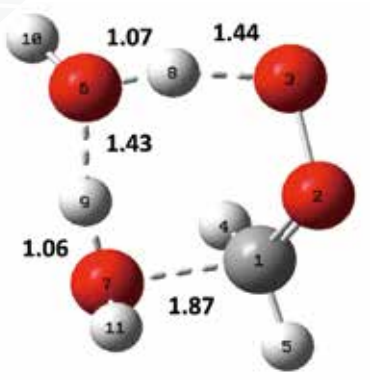
The breakthrough comes from a student from the Department of Chemistry of National Taiwan University, Wen Chao, a junior to be a senior. He was admitted to Prof. Lin’s laboratory as a training student when he was a sophomore, and had successively taken part in the summer research project of the Institute of Atomic and Molecular Sciences, Academia Sinica, and junior college student research project of the Ministry of Science and Technology. Prof. Lin assigned him the research called “Whether Criegee Intermediate Reacts with Water” as his junior college research project. Wen Chao had to start his research from designing the experiment: the first difficulty of which was to have water vapor contained in an apparatus and keep it at a proper concentration, thus rendering the laboratory apparatus appropriate for monitoring Criegee intermediate. Only this procedure had taken him much time. First, in the glass apparatus there must be windows for the probe light to go through, but on which water vapor would meanwhile absorbed, so water vapor and the windows should be appropriately isolated, thus enabling the apparatus to be used in conditions of high water vapor concentration. As a result they applied nitrogen to isolate water vapor and the windows. The next question was how to keep a stable water vapor concentration. Since the evaporation of water is an endothermic process, if the water is not heated, it would become colder, and the pressure of water vapor consequently becomes lower. Through multiple experiments, they finally figure out how to have the apparatus properly heated and an appropriate amount of liquid water evaporated into vapor but not clogging the apparatus. Furthermore, the student and his workmates, Jun-Ting Hsieh, a sophomore at Stanford University and Chun-Hung Chang, a research assistant graduated from the Department of Physics at National Tsing Hua University, had to solve the vibration of the optical table, which affected the monitoring, and consistently improve the detection limit and lower the concentration of Criegee intermediate lest high concentration Criegee intermediate reacts between themselves or with other free radicals.

To everyone’s surprise, the experiment result revealed that Criegee intermediate can react



The above figures are the Criegee intermediate experiment apparatuses

Water vapor gets into the reaction tube through the middle inlet and then is discharged near the two sides. At the ends of the tube there are windows which are isolated from the water vapor and sample gas by nitrogen purge. The advantage of this glass apparatus lies in that with a small caliber of the pipe, a smaller amount of the sample gas is needed, thus making reaching a high gas pressure possible. It is interesting that when Prof. Lin was designing this apparatus, he did not realize this advantage, just accommodating to the size of the parts already-have.



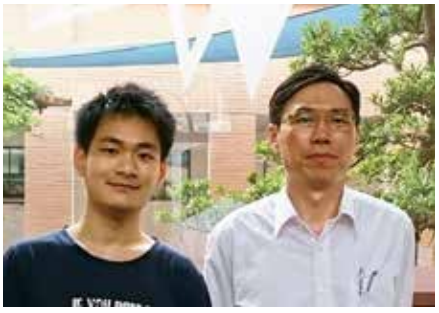
$CH_2OO+(H_2O)_2$ transition state geometry. The atom 1 is carbon; the red spheres represent oxygen atoms; the rest are hydrogen atoms. The bond lengths are in unit of Angstrom.

Citation: Liang-Chun Lin, Master thesis (2016), Department of Chemistry, National Taiwan University.

very rapidly with water, and the reaction rate demonstrates a quadratic dependence on the concentration of water molecules, which means that two water molecules are required to react with one Criegee intermediate. This reaction had been reported based on theoretical calculations in 2004, but observed in experiment for the first time. Prof. Lin then resolved to write an essay on this breakthrough and submitted it to Science. Reviewers at Science were deeply interested in this breakthrough, and offered many suggestions which surpassed the length of the essay itself. Thus it took a long time for the team to do additional experiments and reply. After some ups and downs, eventually, the paper, Direct Kinetic Measurement of the Reaction of the Simplest Criegee Intermediate with Water Vapor, had been published.

Prof. Lin and his team have published on international journals eight articles on Criegee intermediate, from the reaction kinetics of the simplest Criegee intermediate to those of the more complicated. Prof. Lin's research team finds that double-methyl substituted Criegee intermediate does not react with water (a substitution effect) or reacts very slowly with water, but reacts rapidly with sulfur dioxide, which reveals that Criegee intermediate might be a candidate for sulfur dioxide oxidation. In addition, the papers also discuss the reaction types and kinetics of Criegee intermediate of different structures, for example, the reaction with water molecule(s) (monomer or dimer), the thermal decomposition of Criegee intermediate, and the reaction with sulfur dioxide, etc. One of the biggest challenges in future research is "how to synthesize the precursors of Criegee intermediates of different substituent groups".

Prof. Jim Jr-Min Lin switches from his former research on basic molecular beam to the research on free radicals and has established his moderate reputation in atmospheric chemistry. "In the past, the story of how Criegee intermediate reacts was enveloped in mystery, but now half of it has been made clear and the other half remains to be further explored," Prof. Lin says. To Prof. Lin, Criegee intermediate is a new interesting free radical in atmospheric chemistry, and finally a good approach which can synthesize it efficiently, has come out for close investigations. No matter whether it can be put into practical use, its reactivity and molecular structure are special enough to deserve careful study, and the research results would probably find their place in textbooks in the future.



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Religion in Taiwan

How can religion without texts be transmitted?

Since the PRC was established and the Bamboo Curtain was implemented, Taiwan has provided a window into Chinese society and culture (whether real or imagined) for Western researchers in the social sciences and the humanities. However, since 1978 and the beginning of China's "opening up," Taiwan has moved from privileged to marginalized in the political, economic and even academic arenas. Nonetheless, such marginalization has not occurred in the field of religious studies, particularly with respect to Chinese popular religion. Despite some attempts to limit the role of popular religion in Taiwanese society by KMT leaders after the island's retrocession, the traditions and practices that Chinese settlers brought from the mainland in the 18th and 19th centuries have survived and even thrived as they adapted to new conditions, particularly in the wake of Taiwan's industrialization and its "economic miracle" in the 1970s. Improved cross-strait relations between the PRC and the ROC have even led to flows of "traditional knowledge" back to the mainland from Taiwan as restrictions on religious worship have resulted in a surge of interest in popular religion in the PRC.

In this context, Professor Lin's most recent work, Materializing Magic Power: Chinese Popular Religion in Villages and Cities, is an important contribution to the anthropology of religion. In particular, the book's emphasis on the role of statues in materializing deities and their power is significant, as statues also enabled worshippers to enter into wide-ranging relationships with these deities. These relationships are a fundamental feature of popular religion – and a feature that is not limited to Chinese culture – that has been largely overlooked and poorly understood until now, possibly as the result of the generally negative view of "idols" in Abrahamic religions. In this book, Lin discusses how statues are employed to tie gods to a particular village and how personal relationships are constructed between gods and villagers through those statues.

The book on the altar

After the book was published, a copy was placed on the altar to demonstrate how the deity's magical power has spread as far as the United States.

Spirit mediums are a feature of popular religion and have received considerable attention in the literature. However, by focusing on materialization and the agency of objects, Lin is able to describe how mediums – much like statues – act as personalized and localized manifestations of a deity that are fundamental to the god's ability to interact with villagers and participate in their daily lives. Statues and spirit mediums are thus shown to represent a basic distinction between popular religion and other forms of religion, such as Buddhism or Taoism, that have their own clergies and a fixed textual tradition. The power of these materialized deities, a popular topic in the anthropology literature, is also shown to be based on relationships constructed with the community by means of their physical form, whether human or wood.

A deep hollow at the base of Dadaogong's statue, formed from repeated scrapings by devotees

There is a deep hollow at the base of the most efficacious statue of Dadaogong in Wannian where I carried out my fieldwork. This is because when a devotee falls seriously ill, the spirit medium will scrape the bottom of the statue, and boil the scrapings in with Chinese medicinal tea. It is thought that this will increase the potency of the medicine, and help the person recover more quickly. It was not a simple matter to lift the statue and photograph its base. There is a story behind how I obtained this picture. As a result of the repeated scrapings of devotees, the base of the Dadaogong statue in Wannian village had become unstable, and staff at the temple decided to use a piece of steel to seal the bottom of the statue to prevent devotees from gouging it further. In order to take a photo of the hollow that was said to be there, I went to the chairman of the temple committee and asked for special dispensation from him. I was hoping that he would agree to have the metal plate removed so I could take a photo. The chairman considered it, and then told me: "Let's see what the deity thinks." So we went into the temple together. He lit some incense and bowed to the statue and, picking up the divinatory blocks, intoned: "Professor Lin Wei-Ping would like to photograph the base of your statue, in order to show everyone your great powers. Do you agree?" As I listened, my whole body broke out in a cold sweat, and I thought, What if the deity refuses? The blocks fell to the ground, "He's agreed," the chairman said. "He agreed right away, which means he's happy to do it. He wants everyone to know his magical power."

Further, this book offers insights into how the roles of materialized deities (and particularly spirit mediums) have changed in Taiwan in response to urbanization and industrialization. Lin's initial fieldwork was conducted in a rural village in southern Taiwan, and her ethnography details present-day religious practices together with the history of the village and its temples and deities. Her investigation then extends beyond the standard ethnographic scope of a single village to follow the development of local religious practices and the role of spirit mediums among families that migrated from the village to a northern Taiwanese city to find work. In this manner, she shows how new relationships and emotional intimacy – all subsumed under the metaphor of kinship – develop among rural migrants in an urban setting. Perhaps even more significant is Lin's description of how the role of the urban spirit medium has changed, an area that has scarcely been addressed in previous scholarly work on mediums. Lin delves into both ritual details and the thinking that informed the spirit medium's decisions to introduce changes or create new forms of interaction between the deity and believers. In so doing, she shows how the power of the village deity has been delocalized and how popular religion can be understood to have taken a turn towards the personal and the individual, thus mirroring trends that have been termed the "affective turn" or the "subjective turn" elsewhere in the contemporary world.

This shift toward the private or the intimate opens up a wide range of intriguing areas for further study in the field of religion and beyond. However, while noting that such developments are not unique to Chinese society, Lin emphasizes the importance of localizing the global by grounding further research in a firm understanding of fundamental Chinese cultural concepts such as kinship and personhood.

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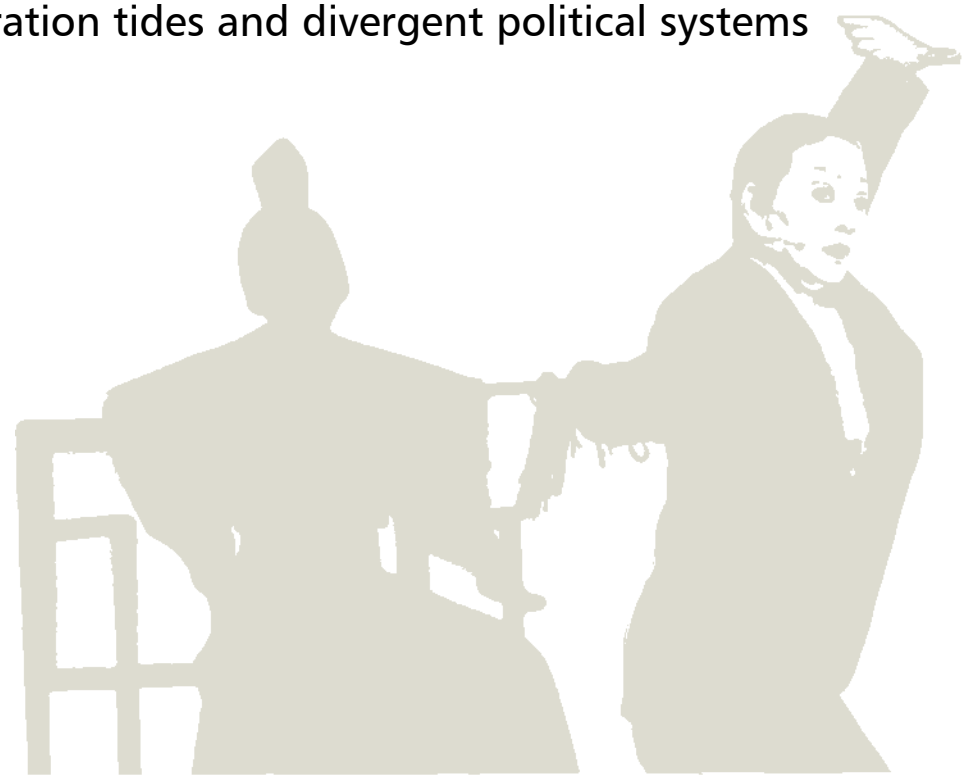
Map of merging — a concise history of Taiwanese theatre

A History of Taiwanese Theatre by Professor Ho-Yi Lin describes the merging trajectories of Taiwanese drama, which has its roots in several migration tides and divergent political systems



Taiwanese drama is a prominent example of the convergence of diverse cultures and political systems. Taiwanese culture – whose history involves ethnic fusion, colonial government, authoritarian regimes, and democracy – absorbed elements of mainland Chinese, Japanese and US-derived Western culture before developing in its own manner. In other words, Taiwanese drama demonstrates the harmony and confrontation of the Western Civilization with the two prevailing Eastern Civilizations. A History of Taiwanese Theatre by Professor Ho-Yi Lin provides concise details for everyone who wishes to explore Taiwanese drama.

Many variables have influenced the development of Taiwanese drama. Professor Lin investigates a substantial number of repertoires and the peaks of their popularity to measure each drama genre's circumstances during every historical period. Furthermore, she uses variables, including demographics, policies, material conditions, social structures and key promoters, to explain each genre's ascension and decline. Among all of these factors, language has played a dominant role, owing to its unusual frequently changing trajectory produced by the ethnic origins of immigrants and a series of political power transfers.

The earliest historical evidence of drama in Taiwan is associated with immigrants from mainland China, before which narrative-oriented performance had yet been developed in the aboriginal community. Before 1784, most of these immigrants came from Quanzhou（泉州）. They brought Nanguan Opera（南管戲）, which had been the prevailing form of drama in their hometowns since the middle of the Ming Dynasty. In 1784, during the Qing Dynasty（清朝）, an important commercial port was constructed in Lukang（鹿港）, thus leading to another wave of immigration. More immigrants from Zhangzhou（漳 州）with a different dialect and distinct

cultural habits flooded into Taiwan. These immigrants brought Beiguan Opera（**北管戲**）, which gradually became more prominent than Nanguan Opera after the Jia-Qin Period（**嘉慶年間**）of the Qing Dynasty.

These waves of immigration not only resulted in ethnic fusion but also produced a subdialect, Taiwanese, that thrived relative to the preexisting dialects of Quanzhou and Zhangzhou. With the accumulation of the folk lyrics and the prosperity of theatre in Taiwan, it was not until the Japanese Colonial Period had a new local opera genre sprouted: Taiwanese Opera（**歌仔戲**; ge-zi-xi）. Taiwanese Opera emerged during the period of Japanese rule over Taiwan（1895-1945）. During that time, the Taiwanese language had already matured and had become the prevalent dialect spoken by the main audience for Taiwanese drama. Therefore, Taiwanese Opera quickly overtook Nanguan Opera and Beiguan Opera because it used the dominant language of Taiwan. Subsequently, Taiwanese Opera maintained its dominance despite Japanese and the ruling Kuomintang policies against local culture. However, the KMT's derogation policy against Taiwanese had incrementally undercut the connection of the language from its people. This decree delivered a crushing blow to Taiwanese Opera, which had already been weakened by the transformation of entertainment after World War II.

In addition to traditional operas, modern theater productions have also appeared in Taiwan since the period of Japanese rule. However, after the R.O.C. government assumed sovereignty over Taiwan in 1946, the KMT party imposed martial law on Taiwan, and used drama to disseminate anti-communism ideology. These policies strictly confined the development of modern theater. However, modern theater related to American/Western culture was embraced by the KMT government. Furthered by key propagandist Man-Kuei Li（**李曼瑰**）, the pro-Western modern theatre using Mandarin grew through Christian associations and colleges and thrived in the 1980s after the government abolished martial law. Subsequently, modern theater became the dominant genre of drama in Taiwan; it continues to maintain this dominance to the present day.

In addition to the Taiwanese Opera and the modern theatre, there have been several other important drama genres in Taiwan, such as Hakka Tea-picking Opera, Taiwanese Glove Puppetry, and even Peking Opera. The Chinese modern drama had showed up briefly in Taiwan during the Japanese Colonial Period. Approximately forty Peking opera troupes had toured Taiwan and thus triggered the motivation of those Taiwanese Beiguan performers who also specialized in Xipi（**西皮**）and Erhuang（**二黃**）to polish their skills. The popularization and spreading of the Drama have evolved from the amateurs troupes of the Qing Dynasty to the Christian associations and societies on campus during the KMT ruling period, and, in particular, the small theatres.

A History of the Taiwanese Theatre, Second Edition absorbs the essence of the research results in Taiwanese Theatre to date, calibrates the clues of migration, development and integration ever since the Dutch rule of Taiwan（1624–1662）until 2013 with succinct information and elegance. This work has already been adopted as a textbook by several drama classes in Taiwanese colleges and universities. Professor Ho-Yi Lin, the author of this classic volume, teaches in the Department of Drama and Theatre of National Taiwan University and has long been dedicated to Taiwanese theatre and associated research.

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Precollege bullying experiences

Linked with health-related quality of life in college

Photo: Dr. Jiun-Hau Huang

Precollege bullying experiences may have long-term effects on college students' health-related quality of life (HRQOL), as measured by the World Health Organization Quality of Life (WHOQOL-BREF) assessment. According to a recent study by researchers at National Taiwan University (NTU), earlier verbal and relational bullying-victimization experiences affected college students' current HRQOL in social relationships and could also affect their psychological HRQOL through depression.

Conducted by Dr. Jiun-Hau Huang, Associate Professor in the Institute of Health Behaviors and Community Sciences, College of Public Health, NTU and his graduate student, Mr. Yu-Ying Chen, this study was published by the American Academy of Pediatrics in the January 2015 issue of Pediatrics, and also reported by Reuters Health. In addition, Dr. Huang's research was featured on the Association of Schools & Programs of Public Health's website in January 2015 and in the Winter 2015 issue of Outlook, the member newsletter of the Society of Behavioral Medicine.

In an effort to communicate the research findings to the public, a press conference was held in the College of Public Health, NTU on January 6, 2015, which was well attended by news reporters and journalists from various media outlets. Dr. Huang was subsequently interviewed again on national radio programs to further discuss the results and implications of this study.

"Precollege bullying-victimization experiences are not something kids simply grow out of once they get to college. Notably, the long-term impact of bullying on their social relationships sometimes goes unnoticed, and they become hidden victims with social difficulties," said Dr. Huang, the study's senior author.

Among 1,439 surveyed Taiwanese college students, 45.7% of them reported ever being bullied. The most common type of bullying-victimization experience was verbal bullying (33.9%), followed by relational (23.4%), physical (11.7%), and cyber bullying (7.2%).

Multiple linear regression models showed that college students with verbal ($\bar{o}$=-.086) and relational ($\bar{o}$=-.056) bullying-victimization experiences, both before and in college, reported significantly lower HRQOL in social relationships. "These victimization experiences may have detrimental effects on interpersonal confidence of the victims, thereby leading to social avoidance and even self-inflicted isolation. The victims could also be marginalized after being bullied," said Dr. Huang.

Interestingly, those with cyber bullying-victimization experiences before college ($\bar{o}$=.060) and in college ($\bar{o}$=.068) reported significantly higher HRQOL in physical health and environment, respectively, suggesting that cyber bullying victimization may have a lifestyle-altering effect. In ad-

dition, the effects of verbal and relational bullying-victimization experiences on psychological HRQOL could be mediated and manifested through depression.

In conclusion, Dr. Huang said, "it is reasonable to suggest that previous exposure to bullying victimization may have latent effects that could be triggered and exacerbated by future bullying-related traumatization. Hence, further research is warranted to elucidate their causal mechanisms and to explore school policies and health education initiatives that may help ameliorate the short-term and long-term effects of bullying on HRQOL."

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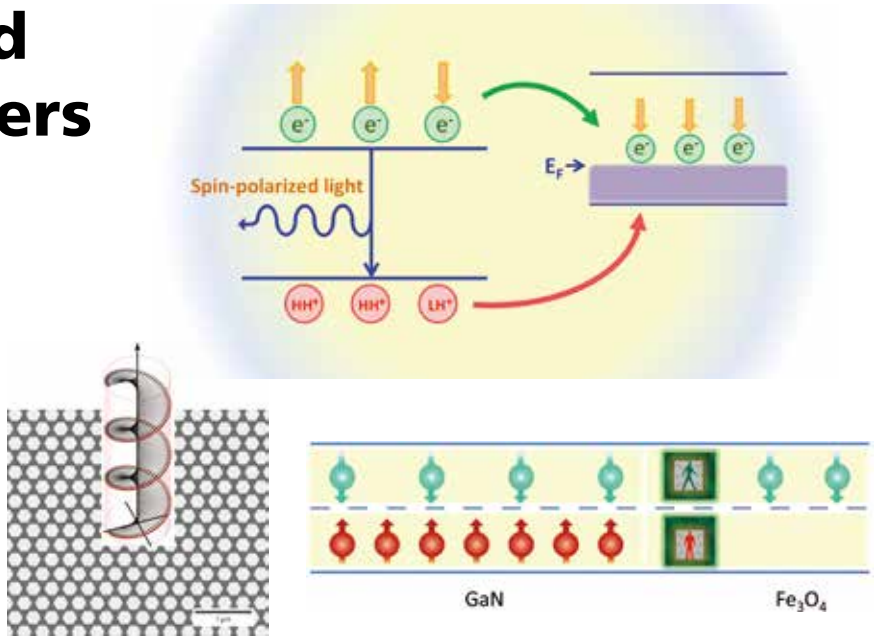
Self-polarized spin-nanolasers



Applications of lasers are ubiquitous in modern society; for instance, lasers are used in optical communication, DVD operation, art, medicine, and the military. Spin-lasers possess not only the specialized properties of conventional lasers but also several features that render them superior to their conventional counterparts. These features, which include reduced threshold currents, enhanced emission intensities, and polarization control with enhanced bandwidths, allow for new applications of lasers, such as in secure communication, chirality studies, high-speed modulators and other advanced optical devices. The most important requirement for generating a spin-polarized laser is the creation of a spin imbalance among electrons in the semiconductor active layer. Currently, the two ways to achieve spin-laser action are electrical pumping by a magnetic electrode and optical pumping by a circularly polarized light source. However, spin injection by a magnetic electrode suffers from poor efficiency due to the spin perturbation produced when spin-polarized electrons pass through the interface between the magnetic electrode and the semiconductor. On the other hand, optical pumping by a circularly polarized light source is unsuitable for practical application. Therefore, progress in the study of spin-polarized lasers has been rather slow.

A recent investigation involved the development of a new paradigm for spin-laser design that does not require electrical pumping by a ferromagnetic spin aligner or optical pumping by a circularly polarized light source. These spin-lasers are created using a composite consisting of nanostructured semiconductors and half-metal nanoparticles. Owing to the suitable band alignment between the semiconductor and the half-metal particles, spin-down electrons and light holes can easily transfer into the half-metal, whereas spin-up electrons and heavy holes remain in the semiconductor. Consequently, a population imbalance in spin-polarized electrons can be achieved via a self-assembled process due to the inherent nature of the band structure. Existing difficulties with spin-lasers can be circumvented by utilizing this new self-polarized spin imbalance mechanism, which has been applied to produce highly efficient light-emitting devices and spin-nanolasers derived from nitride semiconductors. This new mechanism can be applied to many other material systems to generate spin-lasers that cover a wide range of the electromagnetic spectrum, a development that should prove to be extremely useful and timely.

A new paradigm of self-polarized spin imbalance arising from the band alignment between a semiconductor and half-metal nanoparticles; EF is the Fermi level. Spin-down electrons and light holes (LH+) can easily transfer into the half-metal, whereas spin-up electrons and heavy holes (HH+) remain in the semiconductor. The recombination of spin-up electrons and heavy holes will generate spin-polarized light.

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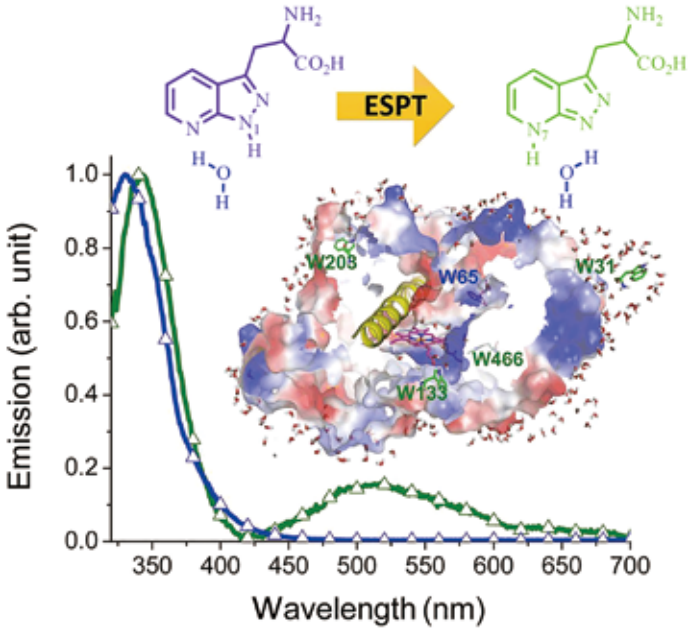
Mapping bio-water in proteins

Using in situ tryptophan analogs to probe water micro-solvation in proteins via water-catalyzed proton transfer reactions

Water molecules within proteins, which have been dubbed "bio-water", play an extremely important role in bioactivities, such as enzymatic reactions, molecular recognition and signal transduction. Scientists have devoted tremendous effort to obtaining a better understanding of these water molecules via indirect measurements, such as molecular dynamic simulation and/or probing the polarity of the local environment. However, a more direct method for sensing and thereby determining the potential functionality of bio-water in proteins remains elusive.

Recently, a team led by Prof. Chou in the Chemistry Department of National Taiwan University (NTU) utilized a novel tryptophan analog, 2,7-diazaindole tryptophan ((2,7-aza)Trp), to successfully detect the presence of water in proteins. This new tryptophan analog exhibits unique properties. In neutral water, (2,7-aza)Trp exists as two proton-transfer isomers: the N(2)-H isomer, which exhibits a 380 nm emission band, and the N(1)-H isomer, which undergoes water-catalyzed excited-state proton transfer (ESPT) that results in an N(1)-H emission band at 340 nm and a prominent green N(7)-H isomer emission at 500 nm. These characteristic multiple emissions offer an unprecedented opportunity to assess water micro-solvation in proteins.



The research team subsequently examined a structurally undetermined protein, "human thromboxane A2 synthase" (TXAS), via the site-specific replacement of five Trp residues with this water-sensitive bio-probe. The lack of N(2)-H emission at 380 nm indicated that water within TXAS is not "bulk water" but is instead more similar to a "water cluster", with the equilibrium of (2,7-aza)Trp markedly shifted toward the N(1)-H isomer. After TXAS was denatured, N(2)-H emission at 380 nm reappeared, suggesting that (2,7-aza)Trp can be used to examine the structural dynamics of protein folding. More importantly, the researchers observed N(1)-H emission at 350 nm and no green N(7)-H emission at 500 nm for (2,7-aza)Trp at the W65 site of TXAS. This result suggests a lack of ESPT and therefore implies that the W65 site is in a water-scant local environment. Conversely, the existence of prominent green (500 nm) emission resulting from ESPT demonstrated that the remaining four examined tryptophan sites in TXAS contact water in their local environments. Thus, the research team has achieved the groundbreaking feat of allowing water environments in a protein to be probed without disrupting the protein's native structure.[1]

The impact of this discovery is far-reaching. Relevant applications have included determining

how water molecules affect the folding, structures and activities of proteins.[2,3]

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Redefining the Taiwan orogeny

Taiwan is located on the Circum-Pacific Seismic Zone; therefore it is disturbed by numerous daily earthquakes due to the convergence and collision between the Eurasian Plate (EP) and the Philippine Sea Plate (PSP). The PSP is in southeastern Taiwan and moves northwest toward the EP at a velocity of 82 mm/year. The EP subducts underneath the PSP in the Huatung Valley, which is located in southeastern Taiwan, and extends south to the Manila Trench. The collision between the two plates forces the island of Taiwan to rise and grow taller via a geologic process known as orogeny.

There exists two different theories for the formation of the Taiwan orogeny. One theory, called the thin-skinned model, states that only the upper crust is compressed and deformed, while there is no interaction with the EP below the PSP. The other theory is called the thick-skinned model, which asserts that both the EP and the PSP take part in the orogeny and are deformed by the collision.

There has been much debate about the two theories. Although evidence supporting each theory has been put forth, both still lack decisive verification. However, this past August, a team from the Department of Geoscience and the Institute of Oceanography at the National Taiwan University (NTU) and the Institute of Earth Sciences at Academia Sinica

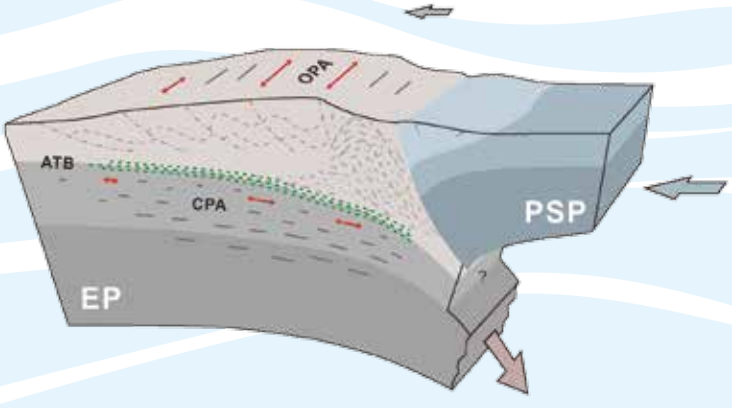

Illustration of the coupled layered deformation zones in the Taiwan orogen. The compressional tectonics and the subduction-dominated deformation are characterized by the orogen-parallel anisotropy and the convergence-parallel anisotropy, respectively. Red double-headed arrows highlight the rapid movement of these two sets of anisotropy. The anisotropy transition boundary (green dots) separates the two deformation regimes and couples the upper crust of the orogen with the subduction zone.

published a paper in Science that explained this long-standing mystery using new technology and observational data.

This paper utilized ambient seismic noises from broadband stations to derive empirical Green's functions that were used to construct a high-resolution three-dimensional model of the seismic anisotropy of Taiwan. From these images, they found that deformation occurred in both the upper and lower plates, similar to the traditional thick-skinned theory. However, the results also revealed that the deformation mechanisms were completely different in the upper and lower crust, similar to the layered phenomenon described by the thin-skinned model. Therefore, neither of the two traditional theories alone could adequately explain the data.

Instead, the research provided a new orogenic model for Taiwan in which the upper crust is dominated by collision-related compressional deformation, whereas the lower crust experiences convergence-parallel shear deformation. This lower crustal shearing was identified as being driven by the continuous sinking of the Eurasian mantle lithosphere when the surface of the subducted plate is coupled with the orogen (Figure 1).

This paper helped to resolve an important mystery in the geological history of Taiwan. Both the upper and lower crust participate in orogeny, although their deformation mechanisms are completely different. The coupled layered deformation mechanism proposed in this research provides an alternative perspective on mountain building and clearly defines the role of subduction in the formation of the Taiwan mountain belt.

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Concealed waves under the sea

The life cycle of the world's most powerful internal waves

There are two types of gravity waves: surface waves at sea level, which can be observed and enjoyed at the beach, and internal waves, which are hidden beneath the surface. Gravity waves are generated at the interface between two media or because of the different densities of two fluids. The interface between the air and the water gives rise to surface waves. Similarly, internal waves are caused by density stratification due to salinity and/or temperature changes of water. The largest internal waves in the world are located in the South China Sea. However, there has been a lack of data for this region due to the challenges related to underwater research. Nevertheless, the energy pattern of internal gravity waves is a key factor for numerical climate models, emphasizing the need for more detailed studies.

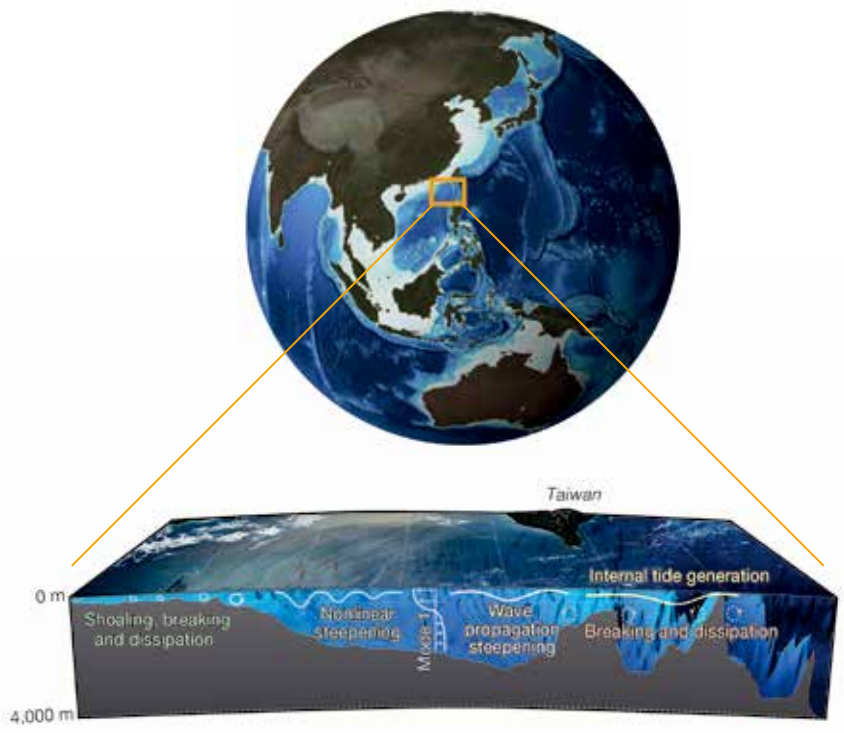
Since 2000 and in collaboration with scientists from the United States, a group from the Institute of Oceanography at National Taiwan University has led a large international project targeting data collection in the South China Sea. Hundreds of researchers, technicians and students have participated in this project, which is supported by the Taiwan Ministry of Science and Technology and the U.S. Office of Naval Research. In May 2015, the achievements of this project were published in Nature, in a paper which was co-authored by 28 researchers from the U.S., Taiwan, Canada, and South Korea. With the help

of this study, the life cycle of the largest known internal waves could be deduced.

This study used in situ data from synthetic aperture radars, mooring, pressure-inverted echo sounders, ship stations, and glider tracks to elucidate the mechanism underlying internal waves. The internal waves generated in the Luzon Strait are related to the surface tide, i.e., a combination of semidiurnal (twice per day) and diurnal (once per day) motions, governed by the sun and the moon. As the waves propagated westward through the Kuroshio Current, energy fluxes of approximately 40 kW/m were measured. This number, which is approximately 100 times larger than typical open-ocean values, exceeds the values known from other generation locations around the globe. Additionally, lee wave[1] phenomena were observed at the ridge of the Batanes Islands at ~121°E. The vertical displacement of the ocean layers reaches up to 500 m. At 115°E, the internal waves dissipate and break because of the shoaling effect of the continental shelf.

In this study, the mechanisms of generating, propagating, steepening, and dissipating the largest internal waves of the world were investigated. The large amount of data collected from numerous sources will provide the basis for future international research and numerical climate models.

1. Lee wave: Atmospheric stationary wave generated by the lee side while passing over a mountain.



Life cycle of the internal waves in the South China Sea

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Precise identification of super tsunamigenic earthquakes over the past 4,000 years in the western Solomon Islands

A strong earthquake can claim the lives of countless people in mere minutes. In collaboration with Professor Fred Taylor of the University of Texas (UT) at Austin, Dr. Chuan-Chou Shen, a Distinguished Professor in the Department of Geosciences of the National Taiwan University (NTU), published new research focused on super earthquakes in the internationally renowned journal "Nature Communications" on June 30, 2015 (ref. 1). According to their article, intertidal coastal coral can act as a seismic recorder and reveals tsunamigenic earthquakes over the past four thousand years in the western Solomon Islands, which is one of six countries in the Pacific Ocean that have diplomatic relations with Taiwan, Republic of China (ROC).

The research team conducted two field trips to Ranongga Island of the western Solomon Islands during May-June and August 2012 to collect intertidal coral fossils, which were sent to the High-Precision Mass Spectrometry and Environment Change Laboratory (HISPEC), which is directed by Dr. Shen. The ages of these fossils were determined using the uranium-thorium radiometric dating method at the HISPEC, NTU. This method has an age precision as high as±11 months.

The ages of the coral fossils indicate that at least four super tsunamigenic earthquakes occurred over the past four thousand years at Ranongga Island. The most recent prehistoric earthquake occurred approximately 750 years ago, and such earthquakes are expected to occur in intervals of approximately 500-1000 years. However, the current dataset suggests an absence of clear periodicity. Local tectonic uplifts induced by prehistoric earthquakes range from 2-3 m, which is higher than the 1.8 m uplift produced by an 8.1 magnitude earthquake in 2007. The 2007 earthquake triggered a tsunami that reached up to 12 m in height and killed more than 50 people. These results indicate that the western Solomon Islands have experienced far larger tsunamigenic earthquakes than the 2007 event!

Researchers searching for intertidal corals on Ranongga Island of the western Solomon Islands.

Reference

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Ranongga Island of the western Solomon Islands.

World-unique coral pyramids

Geoscience researchers prove Micronesia's coral pyramidal tombs are much older than previously thought

Monumental tombs within ancient civilizations worldwide hold precious clues for deciphering the architectural skill, acumen, and industry of prehistoric cultures. In a recent study, the world's only coral pyramidal tombs, which are located in Kosrae, Micronesia, were dated back to 700 years ago by Prof. Chuan-Chou Shen of the High-Precision Mass Spectrometry and Environment Change Laboratory (HISPEC) of the Department of Geosciences of National Taiwan University and his international collaborators. This date is at least three centuries earlier than previous estimates. The study findings, which were published in the journal Science Advances1, also reconstruct the fading prehistoric trans-oceanic culture.

Pyramidal structures dating back to 6,000 years ago provide an important archive of the architectural styles and cultural practices of ancient civilizations. These pyramids often served as tombs for royalty and were built using locally and/or regionally available abiotic materials, such as stone, soil, and clay. The ruins of the prehistoric capital city of Leluh (~AD 1250–1850) in Micronesia contain several royal tombs, which are world-unique pyramids constructed using biotic coral. However, these tombs' construction dates and the means by which the tombs were built had remained shrouded in myth since the discovery of these pyramids.

In the study, Prof. Shen and his team utilized high-precision radiometric uranium-thorium techniques to date three selected sacred Leluh tombs. The team discovered that these tombs were created in the 14th century, approximately 600-700 years ago. The new estimate predates previous estimates by at least 300 to 500 years; in addition, the team found fossil corals with ages of 4,000 to 6,000 years in the tomb structure, refuting previous arguments that only live corals were used in these tombs.

According to oral history, locals built each tomb by forming a chain between the tomb's location and a coastal reef to allow live coral material to be relayed to the construction site. As a result, the tombs were composed of tens of thousands of coral stones, each measuring up to hundreds of centimeters. In contrast to pyramidal tombs from other parts of the world, the Leluh tombs are open and accessible from a truncated top that features a crypt of up to 2 meters by 4 meters. Legends indicate that the reason for this design feature is that the tombs were used only as temporary burial sites, with the king's body placed inside the crypt for praying and worshiping purposes during his funeral. After several months, the royal bones would be relocated to a

Coral sampling atop a Leluh pyramidal tomb.

nearby reef and buried in a deep hole. However, these tales had never previously been validated by scientific evidence.

In a previous study, the remains of a 50-year-old male estimated to have lived during the 1800s were found in one of the tombs. Prior researchers had therefore concluded that the tombs were built approximately 200 years ago. Precise analysis of the coral has demonstrated that the tombs were built in the 14th century; thus, Prof. Shen's team deduced that the 19th-century body belonged to the last king to have participated in the ancient burial ceremony. Although the reason why this king's remains were not relocated is unknown, the study findings validate previous tales indicating that the tombs were repeatedly used as temporary burial sites.

Reference

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Does a warmer ocean guarantee stronger typhoons?

A reinterpretation of tropical cyclone and ocean interaction

Taiwan is located in the northwestern Pacific Ocean and experiences destructive tropical cyclones (TCs; also called typhoons in Asia) every year. Typhoons can cause damage and they have become one of the most popular research topics in Taiwan. Dr. I-I Lin, a professor in the Department of Atmospheric Sciences at National Taiwan University (NTU), has published several important papers that describe new discoveries in the interaction between tropical cyclones and the ocean. These works demonstrate successful national and international cooperation including by researchers from the National Taiwan Normal University (NTNU) and Academia Sinica in Taiwan as well as groups from the USA, China, and Hong Kong.

The condition of the ocean has long been considered a key factor in TC research because of how it may affect TC development and intensification. However, there is still no complete theory that

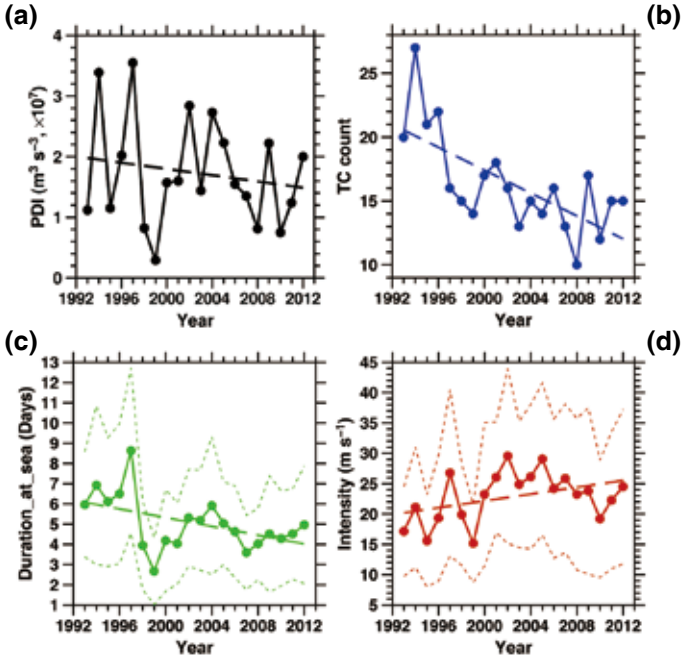

Fig. 1. Time series of the observed PDI and other parameters over the western North Pacific over the past two decades. (a) PDI, (b) annual number of typhoons during the typhoon season (July to October), (c) the average typhoon duration, and (d) the typhoon intensity. [1]

can fully explain TC-Ocean interactions. Traditionally, a warm ocean with a high sea surface temperature (SST) has been assumed to provide a large amount of sensible heat and latent heat, which contributes energy for the TC. Therefore, warmer ocean conditions are believed to nurture more destructive TCs. However, when the TC passes through an ocean, the high wind stress it brings will accelerate the upper ocean layers, mixing in colder water from below and dropping the SST.

Recently, the damage caused by typhoons has been more severe, which is believed to be related to global warming. However, I-I Lin from NTU and Johnny C.L. Chan from the City University of Hong Kong published an article in Nature Communications in 2015 [1] stating that typhoon destructive potential has decreased in recent decades. They found that the high SST provides a favourable environment for typhoon development and dramatically strengthens typhoon intensity, as expected. However, at the same time, the annual number of TCs during typhoon season and the average TC duration have decreased (Fig. 1). This is believed to be because, under global warming, atmospheric circulation is strengthened. Therefore, both the lower-tropospheric easterly trade winds and the upper-tropospheric westerlies are enhanced and the vertical wind shear (the difference between the two) is increased. The increased vertical wind shear, along with a decrease in the low-level relative vorticity in the typhoon genesis region, creates poor atmospheric conditions for typhoon formation and results in fewer typhoons per season.

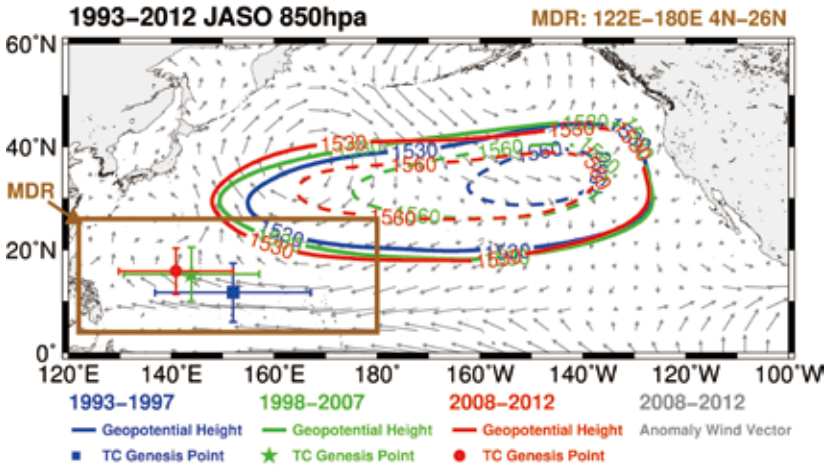

Fig. 2. The averaged typhoon genesis positions (with 1 standard deviation) over three different periods in the past 20 years (1993-2012) and the strengthening of the subtropical high at 850 hPa. [1]

To adjust to these new conditions, the genesis position of typhoons was found to shift to the northwest, as shown in Fig. 2. When a TC forms farther westward, the path that it travels is shorter than normal, resulting in the lower durations observed. This pattern is also supported by the 35% decrease of the Power Dissipation Index (PDI) in recent decades, as shown in Fig. 1. The PDI is a quantified index of the destructive potential of typhoons and includes interactions among typhoon frequency, duration and intensity. Under a global warming scenario, the PDI could decrease by as much as 15%.

Another study, also published in Nature Communications by Taiwanese-Chinese collaborators [2], found that the ocean conditions may suppress the intensification of TCs under global warming. The authors investigated outputs from 22 climate models under a global warming scenario and focused on the western North Pacific (WNP) and the North Atlantic (NA) regions. The research focused on the ocean cooling effect (OCE) produced when a TC passes over the ocean, allowing strong winds to mix colder subsurface (deeper) water with water near the surface. Such mixing reduces the SST and decreases the available air-sea sensible and latent heat fluxes. In addition, because the subsurface ocean temperature warms more slowly than the surface ocean, under global warming, a steeper vertical tem-

perature gradient is expected. As a result, the OCE will be even more effective at decreasing SST under global warming. While the OCE is a function of the initial vertical temperature profile of the ocean and the particular TC conditions, any expected strengthening of the cooling effect will in turn prevent TC intensification.

There is a final interesting research report, published by a Taiwan-USA partnership in Scientific Reports, which addresses the typhoon-El Niño relationship [3]. During El Niño, the eastern Pacific is warmer than normal, providing a favourable location for TC genesis and causing a positive feedback for TCs. The TC genesis region shifts southeastward, and any resulting TC would travel a longer distance before it dissipates. Consequently, a TC could achieve a higher intensity during El Niño. However, this research identified a negative feedback to TC intensification that works as a damper to restrain typhoons from becoming over-intensified. During El Niño, there is a strong pre-existing subsurface shoaling over the western North Pacific Ocean, and the subsurface water is much colder than in normal years. The stronger OCE during El Niño reduces the heat flux supplied to TCs, providing a damper on TC intensification. A schematic of this Gaia[i]-like process, in which different Earth mechanisms help to maintain stable conditions, is shown in Fig. 3.

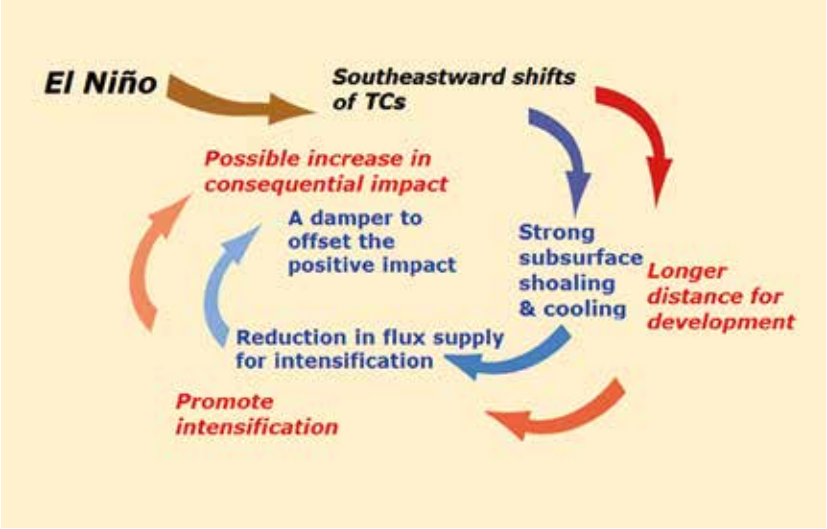

Fig. 3. Schematic of the Gaia-like mechanism in the El Niño-TC relationship. [3]

The formation of TCs is related to both atmospheric and oceanic conditions. These studies have analysed huge amounts of climate data and have shown how complex these interactions can be. However, the new interpretations of TC-ocean interaction can lead to a better understanding of how and when TCs will evolve.

i. Gaia: a hypothesis stating that there are self-regulation mechanisms among the organisms and inorganic surroundings on Earth, which work to keep our planet suitable for life.

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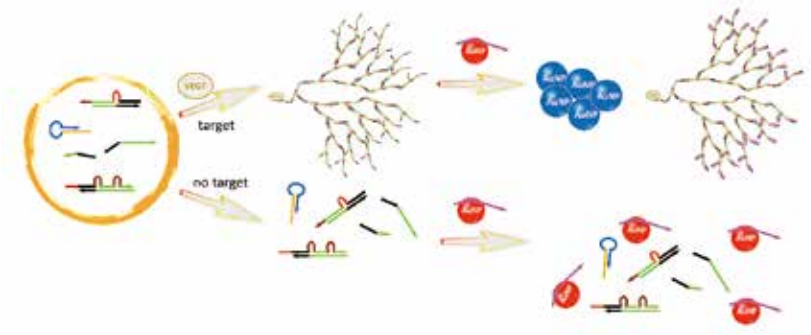
An enzyme-free colorimetric assay for the rapid detection of specific target proteins

A label - and enzyme - free colorimetric sensing platform for the amplified detection of target proteins was developed based on the ingenious combination of a nonlinear hybridization chain reaction system and a gold nanoparticle aggregation strategy

The combination of gold nanoparticles (AuNPs) and DNA has a history that spans two decades with potential applications as biosensors in biomedicine. Now, Prof. Chii-Wann Lin's group from the Institute of Biomedical Engineering have identified a new method for using AuNPs with DNA that takes advantage of a technique called nonlinear hybridization chain reaction (NHCR), which refers to the formation of dendritic DNA nanostructures through a self-sustained, branching growth mechanism.

Here, these researchers developed a method to control the assembly of AuNPs using a similar nonlinear hybridization chain reaction technique. DNA aptamers selected to bind specific molecules show promise for the development of NHCR triggers that initiate a chain reaction only in the presence of the target molecule. A programmed DNA dendritic nanostructure is formed via a target-assisted cascade amplification reaction using two double-stranded DNA substrates and two single-stranded auxiliary DNA molecules as assembly components, and the resulting dendritic nanostructure is subsequently captured using DNA-sensing probe-stabilized AuNPs. The release of the sensing probes from the AuNPs results in the formation of unstable AuNPs, promoting salt-induced aggregation. Prof. Lin and co-workers have used this aptamer-trigger concept to specifically detect vascular endothelial growth factor (VEGF). This assay does not require time-consuming AuNP surface modification and enzymatic amplification steps. Additionally, this assay requires less than an hour for completion compared with DNA-based linear amplification detection, which takes several hours to complete. Prof. Lin remarked, "If we succeed in developing a general aptamer triggering mechanism for biosensing, then NHCR amplification could be incorporated in sensors for a wide range of biomolecules."



Colorimetric detection of VEGF using DNA sensing probe-stabilized AuNPs

Prof. Lin's group also currently works with mobile platforms for on-site testing and healthcare. Thus, in the future, this technique could be applied for point-of-care quantitative detection using a smartphone-based device.

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A new method for detecting urinary biomarkers of DNA damage induced by acrylamide exposure via tobacco smoke and diet

A collaborative research study between professors at National Taiwan University and researchers across universities in Taiwan[i] provides the first quantitative analysis of a new risk-associated biomarker for acrylamide exposure from tobacco smoke and diet.

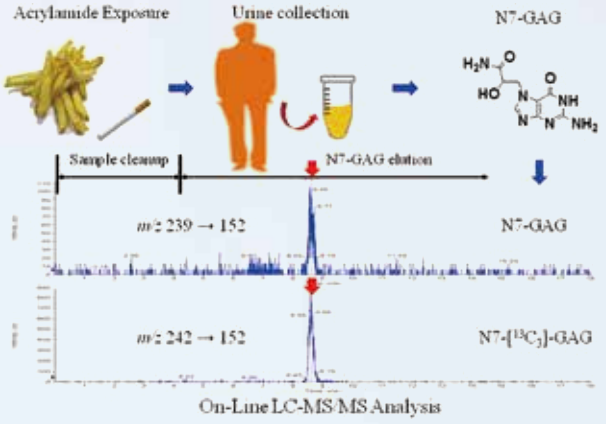
Background information

Acrylamide (AA) is an industrial chemical widely used in the production of polymers and copolymers for many applications. In addition to occupational exposure, the general public might also be exposed to AA from the consumption of foods processed at high temperatures and from cigarette smoking. Exposure to AA has been found to be associated with neurotoxicity and reproductive toxicity. On the basis of evidence established by animal studies and inconclusive epidemiology studies, the International Agency for Research on Cancer has classified AA as a probable human carcinogen (Group 2A). The current understanding of the mechanism by which AA causes cancer suggests that absorbed AA can be metabolically converted to glycidamide (GA), which reacts with DNA bases and forms DNA adducts, thus leading to potential DNA damage and cancer. Among the nine identified AA-induced DNA adducts in mice, N7-(2-carbamoyl-2-hydroxyethyl)-guanine (N7-GAG) is the most abundant adduct. Although N7-GAG has not been analyzed in DNA from human tissue, this segment might be depurinated to form purine sites in the DNA backbone and subsequently excreted in the urine. Because urine samples are easy to assess through non-invasive methods, the urinary DNA adducts might serve as exposure indicators and potential cancer risk-associated biomarkers in molecular epidemiology studies.

About the research

NTU professors and researchers from other universities conducted a study entitled "Potential Association of Urinary N7-(2-carbamoyl-2-hydroxyethyl)-guanine with the Dietary Acrylamide Intake of Smokers and Nonsmokers", which was recently published in Chemical Research in Toxicology. To confirm the genotoxicity of AA and its active species in humans, Professor Kuen-Yuh Wu and colleagues have developed a method to analyze urinary N7-GAG to assess AA exposure from tobacco smoke and dietary intake. Urinary samples were collected from smokers and non-smokers with no history of occupational exposure to AA. Isotope-dilution liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) was used to analyze the samples. Other metabolites, such as urinary AAMA and cotinine, were also measured by using LC-MS/MS, and statistical comparisons with the levels of urinary N7-GAG were performed to provide a better understanding of the association between this metabolite and dietary exposure to AA.

Wu and his team have found that urinary N7-GAG is associated with solely AAMA, thus implying that AAMA might also serve as a surrogate biomarker for DNA damage induced by AA exposure. The urinary N7-GAG of non-smokers and smokers is significantly associated with a low level of dietary AA intake. Their results confirm that the urinary N7-GAG of smokers and non-smokers is caused by exposure to AA, either through food consumption or tobacco smoke exposure. Wu and his team have also found that N7-GAG formation in non-smokers without an occupational exposure history most probably reflects the consumption of foods processed at high temperatures. The mechanisms underlying the carcinogenicity of AA remain unclear; however, these results, which demonstrate an association between the urinary excretion of N7-GAG and recent exposure to AA, indicate a new mechanism by which AA causes cancer (i.e.,



Published in: Chih-Chun Jean Huang; Chia-Fang Wu; Wei-Chung Shih; Yu-Syuan Luo; Ming-Feng Chen; Chien-Ming Li; Saou-Hsing Liou; Wen-Sheng Chung; Su-Yin Chiang; Kuen-Yuh Wu; Chem. Res. Toxicol. 2015, 28, 43-50.

DOI: 10.1021/tx500265p

potential genotoxicity via DNA alkylation). The newly developed analysis of urinary N7-GAG is a non-invasive method to measure DNA alkylation by GA, and N7-GAG may be a valuable biomarker for confirming the active metabolite of AA responsible for DNA alkylation, which results in mutagenicity in humans. In addition, N7-GAG might also serve as a chemical-specific and potential risk-associated biomarker in molecular epidemiology studies.

i. Kuen-Yuh Wu*, Wei-Chung Shih, Yu-Syuan Luo (Department of Public Health & Institute of O ccupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taipei 10055, Taiwan); Chih-Chun Jean Huang (Department of Food Science, National Pingtung University of Science and Technology, Neipu, Pingtung 91201, Taiwan); Chia-Fang Wu, Ming-Feng Chen, Chien-Ming Li, Saou-Hsing Liou (Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Zhunan Town, Miaoli County 35053, Taiwan); Wen-Sheng Chung (Department of Applied Chemistry, National Chiao Tung University, Hsinchu 30010, Taiwan); Su-Yin Chiang* (School of Chinese Medicine, China Medical University, Taichung 404, Taiwan).

Reference

Chih-Chun Jean Huang, Chia-Fang Wu, Wei-Chung Shih, Yu-Syuan Luo, Ming-Feng Chen, Chien-Ming Li, Saou-Hsing Liou, Wen-Sheng Chung, Su-Yin Chiang, and Kuen-Yuh Wu. (2015). Potential association of urinary N7-(2-carbamoyl-2-hydroxyethyl) guanine with dietary acrylamide intake of smokers and nonsmokers. Chemical Research in Toxicology 28, 43-50. DOI: 10.1021/tx500265p.

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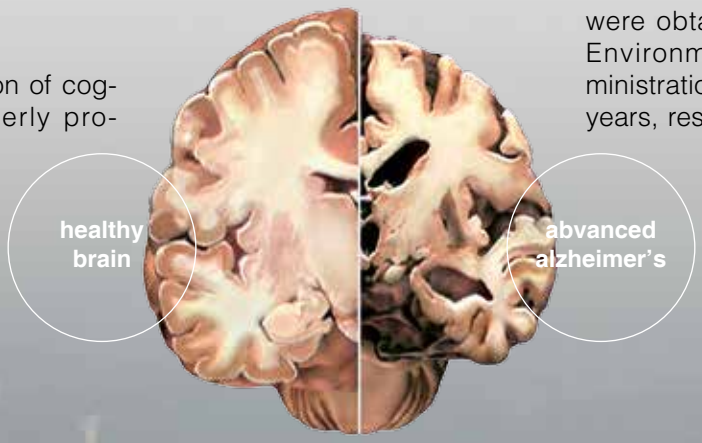
Air pollution and dementia risk

Long-term exposure to particulate matter<10 μm (PM_{10}) and ozone increases the risk of developing Alzheimer's disease and vascular dementia in the elderly

Evidence suggests that exposure to air pollution induces changes in the brain. In a new study of elderly people living in northern Taiwan, researchers from National Taiwan University found that long-term exposure to airborne particulates and ozone increases the risk of developing Alzheimer's disease (AD) and small-vessel vascular dementia (VaD) by two-fold to fourfold. This work has been selected as a Special Invited Article[1] with a featured video[2] and an Invited Commentary[3] for publication in an open access journal of the Alzheimer's Association, USA.

"Only a small portion of cognitively impaired elderly progress to dementia each year. Therefore, studies of cognitive impairment have been unable to fully explain the association between air pollution and the risk of dementia," explained lead investigator Dr. Yen-Ching Chen. "To the best of our knowledge, this is the first case-control study to assess the association between longitudinal air pollution [particulate matter (PM) and ozone] exposure with clinically diagnosed dementia (AD and VaD)." Currently, there is no cure for dementia, and a better understanding of the association between air pollutants and dementia will be helpful in unraveling the complex etiology of dementia.

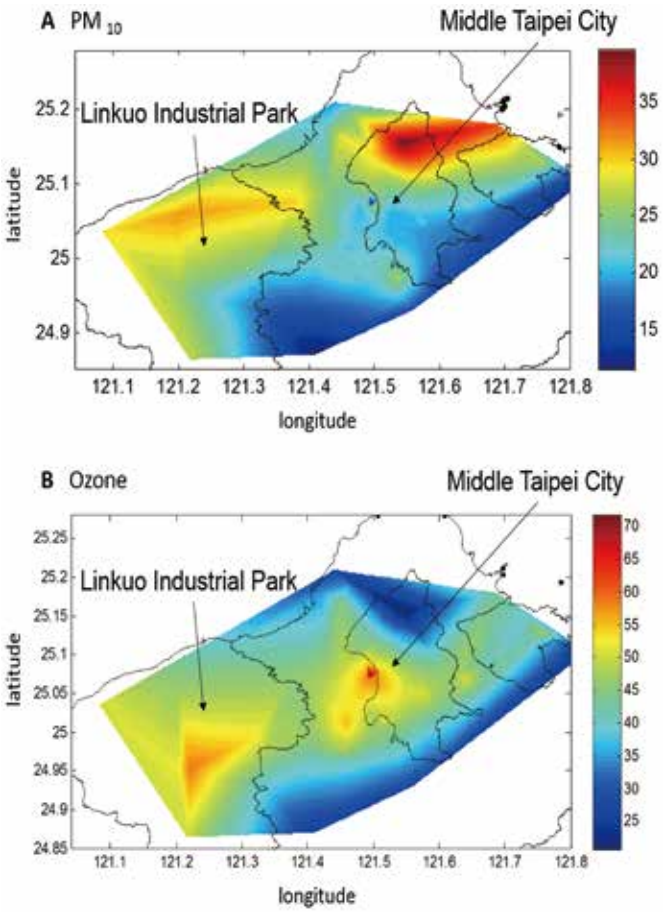
This case-control study comprised 249 AD patients, 125 small-vessel VaD patients, and 497 controls recruited from three teaching hospitals in northern Taiwan from 2007 to 2010. All participants were aged 60 years or older. "The long-term exposure data are especially important because the progression of dementia is slow, which may not be easily explained by short-term exposure," says Dr. Chen. Therefore, PM_{10} and ozone data were obtained from the Taiwan Environmental Protection Administration (EPA) for 12 and 14 years, respectively. A spatiotem-



poral tool (Bayesian maximum entropy) was used to estimate the individual exposure level of air pollutants.

Long-term exposures to ≥ 49 μg/m^3 of PM_{10} (Taiwan 24-hr standard: 125 μg/m^3; annual standard: 65 μg/m^3) and ≥ 22 ppb of ozone (Taiwan 8-hr standard: 60 ppb) were significantly associated with increased risks of AD (highest vs. lowest tertile of PM_{10}: adjusted odds ratio (AOR) = 4.17; highest vs. lowest tertile of ozone: AOR = 2.00). Similar findings were observed for VaD. In addition, this study was the first to reveal a dose-response relationship between PM_{10} and the risk of AD and VaD.

Published papers on air pollution and health outcomes will be considered by the EPA to determine standards. "This study found a significant increase in dementia risk despite the long-term exposure to air pollutants with levels below the current standard. Therefore, it is important to clarify the role of air pollutants on the occurrence of dementia, and studies evaluating this association have been lacking. Future studies are warranted to explore the role of other air pollutants in the etiology of AD and VaD," noted Dr. Chen. This study is therefore a crucial starting point for future work on the effect of air pollution and the risk of dementia.



Maps showing the average annual PM_{10} exposure over 12 years (A) and the average annual ozone exposure over 14 years (B) in northern Taiwan.

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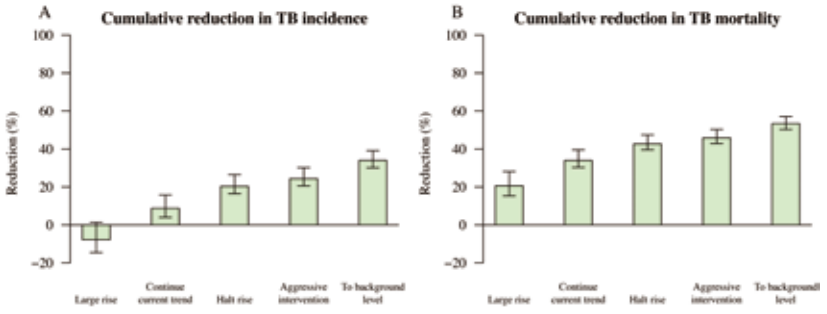
Diabetes prevention may benefit the control of tuberculosis worldwide

The increasing prevalence of diabetes may severely impair the efficacy of tuberculosis control in countries with a high burden of tuberculosis.

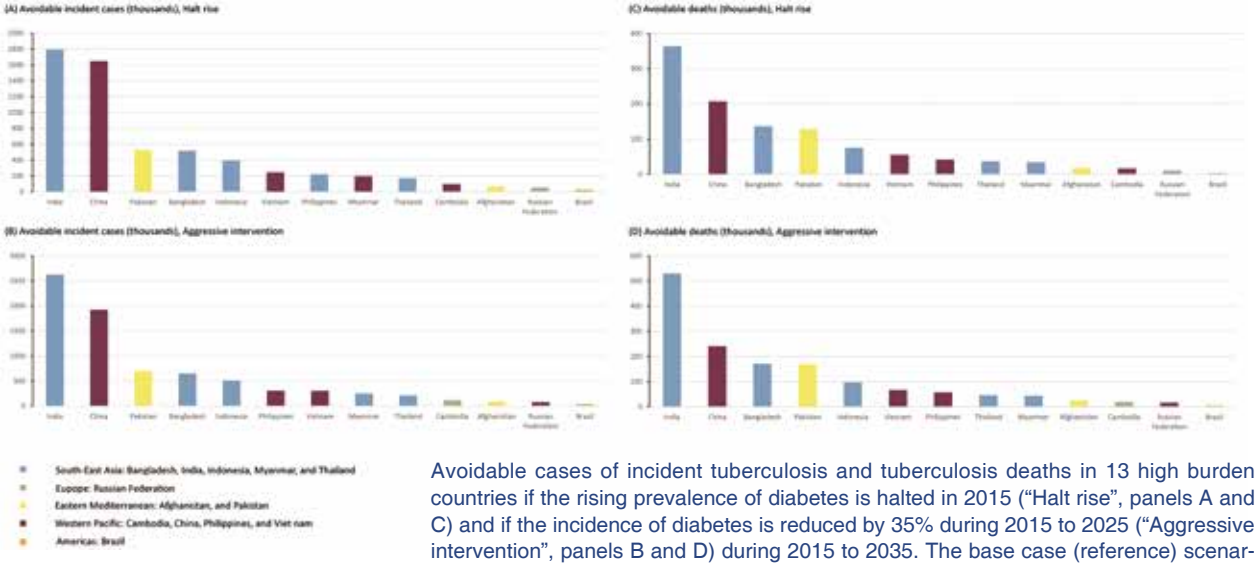
The diabetes epidemic may substantially affect tuberculosis epidemiology in high-burden countries, according to a new study by researchers at the National Taiwan University (NTU). The World Health Organization (WHO) aims to reduce the incidence of tuberculosis by 90% and mortality by 95% by 2035; therefore, this study, which was published online in March 2015 in The Lancet Diabetes & Endocrinology, explored factors that may affect the global tuberculosis control strategy.

Conducted by Dr. Hsien-Ho Lin and Dr. Chi-Tai Fang, associate professors of epidemiology and preventive medicine at the College of Public Health (CPH), NTU, and their colleague, Dr. Sung-Ching Pan at the National Taiwan University Hospital (NTUH), this study explored whether the increasing prevalence of diabetes would affect tuberculosis control in high-burden countries. Mathematical modeling was used based on the available knowledge regarding the global epidemiology of diabetes and tuberculosis to project the different effects of future tuberculosis incidence and mortality within the 13 high-burden countries through different diabetes prevalence settings.



The cumulative reduction of tuberculosis incidence (A) and mortality (B) in 13 countries with high tuberculosis (TB) burdens under different scenarios of diabetes prevalence, 2015–2035.

If the prevalence of diabetes continues to increase in these 13 countries, as it has over the past decade (base case scenario), by 2035, the cumulative reduction in tuberculosis incidence would be 8.8% (95% credible interval



Avoidable cases of incident tuberculosis and tuberculosis deaths in 13 high burden countries if the rising prevalence of diabetes is halted in 2015 (“Halt rise”, panels A and C) and if the incidence of diabetes is reduced by 35% during 2015 to 2025 (“Aggressive intervention”, panels B and D) during 2015 to 2035. The base case (reference) scenario assumes that the prevalence of diabetes will continue the current rising trend.

[CrI] 4.0–15.8) and the mortality would be 34.0% (30.3–39.6). Compared with the base case scenario, halting the increase of diabetes would avoid 6 million incident tuberculosis cases (95% CrI 5.1–6.9) and 1.1 million tuberculosis deaths (1.0–1.3) in these 13 countries over 20 years. If interventions reduce the diabetes incidence by 35% by 2025, 7.8 million (6.7–9.0) tuberculosis cases and 1.5 million (1.3–1.7) tuberculosis deaths could be averted by 2035.

"The diabetes epidemic could substantially affect tuberculosis epidemiology in high-burden countries," the authors write. "The communicable disease and non-communicable disease sectors need to move beyond conventional boundaries and link with each other to form a joint response to diabetes and tuberculosis.

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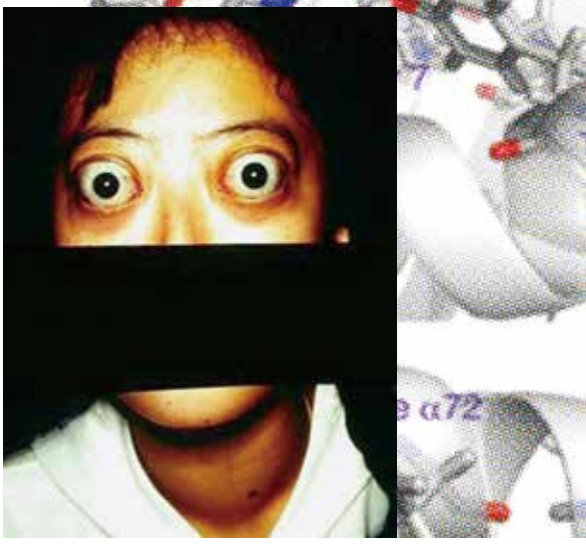
In search of a gene

Two HLA gene loci associated with anti-thyroid drug-induced agranulocytosis



Graves' disease is the leading cause of hyperthyroidism, which affects approximately 1%-1.6% of the general population. Graves' disease primarily results from circulating autoantibodies that target thyroid-stimulating hormone (TSH) receptors on the thyroid gland. After these antibodies bind TSH receptors, the thyroid gland produces and secretes excessive thyroid hormone. Individuals with Graves' disease may present with body weight loss, palpitation, hand tremor, enlarged thyroid gland, and even bulging eyes.

Medical treatment for Graves' disease includes anti-thyroid drugs and radioactive iodine. However, if medical treatment fails, then surgical resection should be considered. Anti-thyroid drugs include methimazole, carbimazole and propylthiouracil, which suppress excessive hormone production by the thyroid gland to achieve clinical remission.

Thus, anti-thyroid agents are the cornerstones of Graves' disease treatment.

However, some patients develop deadly agranulocytosis after treatment with these agents. So-called agranulocytosis, defined as an absolute neutrophil count of less than 500/mm^3, leads to the breakdown of the immune system. Once developed, the risk of severe infection and mortality markedly increases.

Can the onset of agranulocytosis be predicted after administering anti-thyroid drugs?

In July 2015, Professor Chang

and his team published a study concerning the genes associated with anti-thyroid drug-induced agranulocytosis in Nature Communications.

How were the relevant genes identified?

Human Leukocyte Antigen (HLA) should be considered when examining the gene-associated adverse effects of drugs. Located on chromosome 6, HLA shows high variation and is closely associated with immune function, autoimmune disease and some adverse drug effects. In addition, non-HLA genes may affect the metabolism of drugs and have also been associated with the side effects of these compounds.

In this study, direct HLA loci genotyping and a genome-wide association study (GWAS) were employed to analyze genetic differences between individuals with and without agranulocytosis. Direct HLA loci genotyping focuses on differences in HLA alone, whereas GWAS analyzes single nucleotide polymorphisms (SNPs) throughout the entire genome.

These efforts led to the identification of two loci that are highly associated with anti-thyroid drug-induced agranulocytosis: HLA-B*38:02 and HLA-DRB1*08:03. The estimated odds ratios for these two loci, when comparing allele carriers with non-carriers, were 21.48 and 6.13, respectively. Moreover, individuals carrying both HLA-B*38:02 and HLA-DRB1*08:03 show an increased risk of up to 48.41.

These results may guide the decision-making of clinicians in Asia. After diagnosis, doctors can arrange for genetic testing prior to initiating treatments with these compounds. However, when the two HLA loci described above are detected, an alternative treatment should be considered to avoid agranulocytosis.

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Pei-Lung Chen, Shyang-Rong Shih, Pei-Wen Wang, Ying-Chao Lin, Chen-Chung Chu, Jung-Hsin Lin, Szu-Chi Chen, Ching-Chung Chang, Tien-Shang Huang, Keh-Sung Tsai, Fen-Yu Tseng, Chih-Yuan Wang, Jin-Ying Lu, Wei-Yih Chiu, Chien-Ching Chang, Yu-Hsuan Chen, Yuan-Tsong Chen, Cathy Shen-Jang Fann, Wei-Shiung Yang & Tien-Chun Chang. Genetic determinants of antithyroid drug-induced agranulocytosis by human leukocyte antigen genotyping and genome-wide association study. Nat. Commun. 6:7633 DOI: 10.1038/ncomms8633 (2015).

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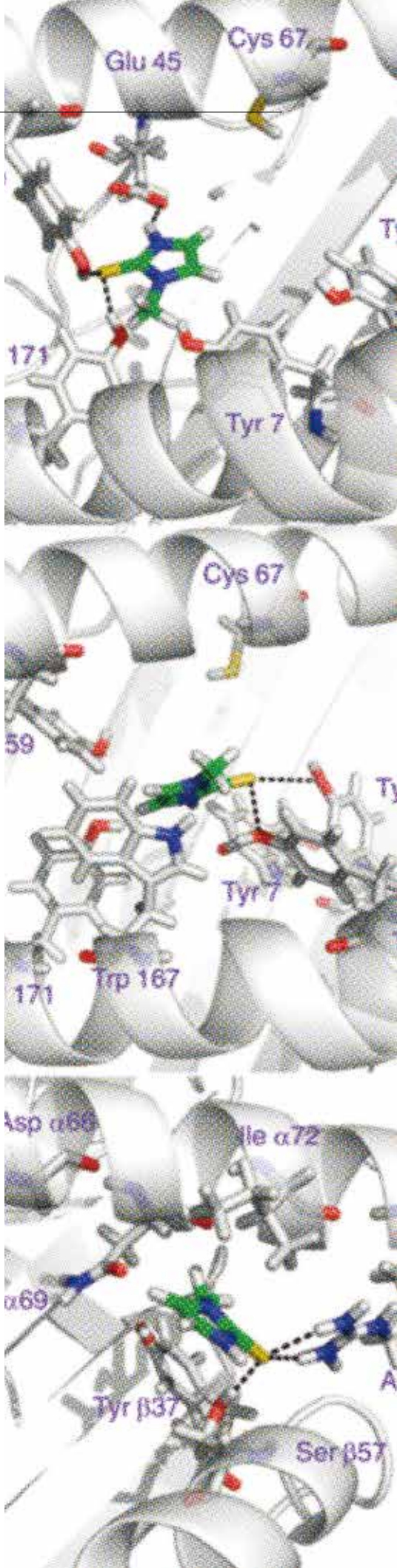


To stop or not to stop

Unraveling the mystery of the continuous and discontinuous transcription of coronaviruses

In the past, human coronaviruses were considered common pathogens for mild upper respiratory tract infections. However, in recent years, new coronavirus pandemics, including severe acute respiratory syndrome (SRAS) and Middle East respiratory syndrome (MERS), have claimed many lives with high mortality rates. Because coronavirus pandemics pose an increasing threat in human society, drug development is an urgent issue.

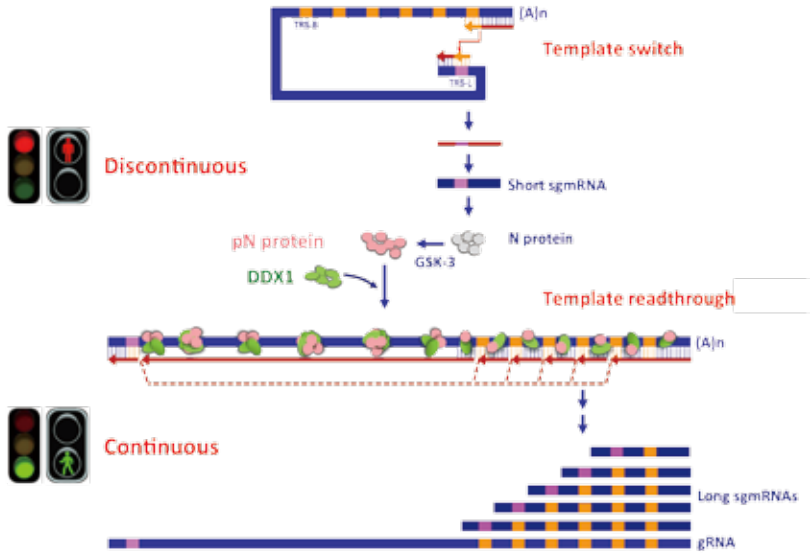
However, before a discussion of the development of novel antiviral agents occurs, a detailed understanding of the coronavirus replication cycle is necessary.

Coronaviruses are enveloped viruses with positive-sense, single-stranded RNA genomes. As one of the largest RNA viruses, the genome size of coronaviruses is approximately 30,000 base pairs. After the viral particles enter host cells, the genomic RNA is released into the cytosol and translated into nonstructural viral proteins essential for viral replication, including RNA polymerase. The viral RNA polymerase subsequently synthesizes several subgenomic RNAs of different lengths, which predominantly encode the viral structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, for subsequent virion assembly and release.

With only one viral genomic RNA template, how can the RNA polymerase generate several subgenomic RNAs of different lengths?

The production of subgenomic RNAs is not achieved through post-transcriptional splicing. Instead, these RNA molecules are generated through the base pairing of the specific body transcription regulatory sequence (TRS), located in front of each structural gene, with the complementary leader TRS at the 5'-UTR of the viral genome. During the synthesis of negative-stranded RNA, the viral RNA polymerase recognizes the body TRS and initiates a template switching event. This unique process, referred to as "discontinuous transcription", is a unique characteristic of coronaviruses. Whenever the polymerase encounters a TRS, it determines whether to stop for shorter subgenomic RNAs or to

From Discontinuous to Continuous Transcription of Coronaviruses



proceed for longer subgenomic or even genomic RNAs.

However, the mechanism underlying this determination is poorly understood.

In October 2014, Professor Yeh and Dr. Wu published a study in Cell Host & Microbe on the mechanisms underlying the transition from discontinuous to continuous transcription in coronaviruses.

The research team first implicated the glycogen synthase kinase-3 (GSK-3) in host cells as responsible for viral nucleocapsid phosphorylation. GSK-3 inhibition selectively reduces the generation of genomic RNA and longer subgenomic RNAs, but less effect on shorter subgenomic RNAs. Thus, these authors proposed that the phosphorylated nucleocapsid protein plays an important role in regulating the transition from discontinuous to continuous transcription.

In addition, these authors also reported that phosphorylated nucleocapsid recruits the cellular RNA helicase, DDX1, for binding with the viral genome, facilitating the read-through of templates and enabling the synthesis of longer subgenomic RNAs.

This study sheds light on the key mechanisms underlying the continuous and discontinuous RNA synthesis in coronaviruses. Because this mechanism is conserved among most coronavirus species, including SARS-CoV and MERS-CoV, it has become a potential target for novel antiviral drug development.

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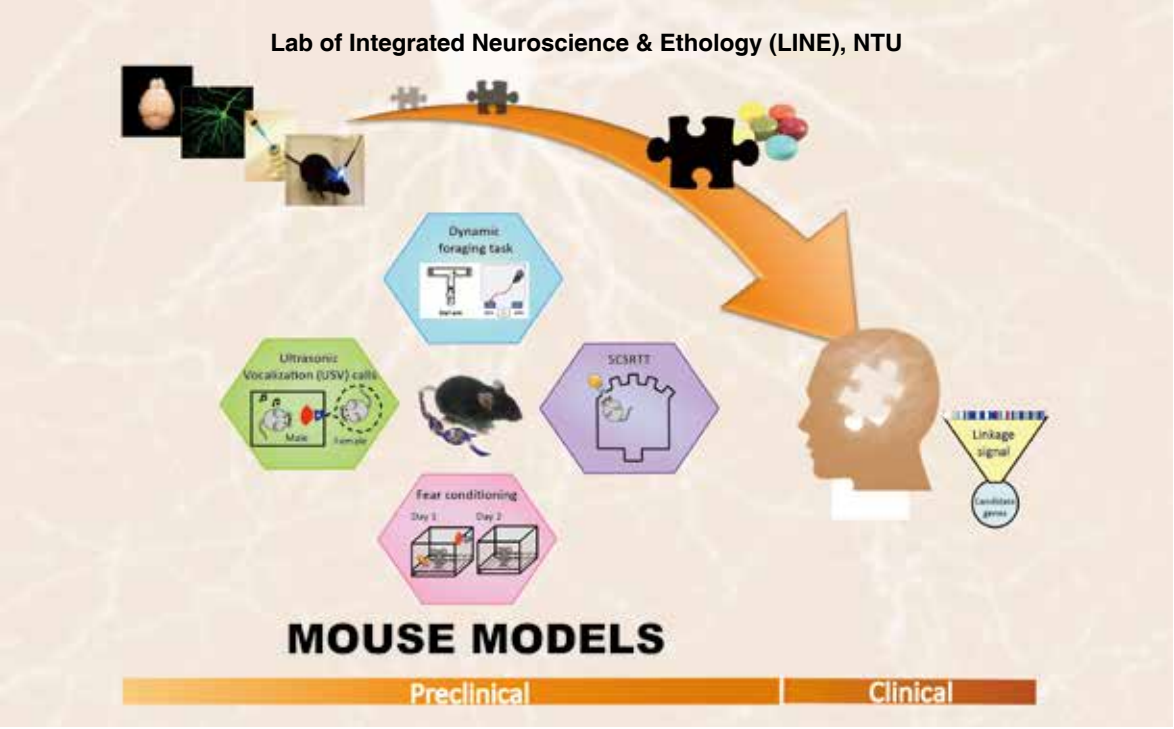
Assessing schizophrenia-relevant deficits and treatments in mice

Mouse models of neuropsychiatric disorders have been an indispensable tool for studying pathological mechanisms and for the in vivo testing of novel therapeutic agents

As noted by Nobel Laureate Dr. Eric Kandel in 2009, "Understanding the biology of mental illness would be a paradigm shift in our thinking about mind... it would also tell us more about who we are and how we function." Schizophrenia is a severe mental disorder, with tremendous cost to our society. The extended timeline and high attrition rate make drug development for schizophrenia (and other psychiatric disorders) an expensive and risky business. The negative and cognitive symptoms of schizophrenia represent an unmet medical need for antipsychotic development. Schizophrenia and other psychiatric disorders are generally diagnosed based upon a collection of symptoms that are defined by the combination of an individual's feelings, perceptions, and behaviors. The exact causes of schizophrenia remain elusive, although both genetic predisposition and environmental risk factors play crucial roles in its development, especially before young adulthood.

As a complement to human studies, animal models not only provide a practical approach to elucidating causal relationships between genes and related symptoms but also play an indispensable role in the discovery and verification of potential drugs and treatments. Although



An illustration of the basic ideas and concepts for assessing schizophrenia-relevant phenotypes and treatments in mice in the Laboratory of Integrated Neuroscience and Ethology (LINE) at National Taiwan University (Image credit: Wei-Li Hung).

it is nearly impossible to capture the full phenotypic spectrum of schizophrenia in mice, the major role of behavioral tests in mice has been to provide insights into the underlying neurobiological mechanisms and the development of new therapeutics for schizophrenia. Given that the recovery of cognitive and social abilities significantly benefits functional outcomes, there has been increasing interest in characterizing cognitive and social functions in normal mice as well as genetically engineered mice.

The Laboratory of Integrated Neuroscience and Ethology (LINE, http://www.psy.ntu.edu.tw/LINE/), led by Dr. Wen-Sung Lai in the Department of Psychology at the National Taiwan University, has established a comprehensive behavioral test battery and the required equipment (including over 500 individually ventilated cages for animal housing) to conduct functional assays and drug screening in mice. This laboratory also provides technical support for preclinical drug screening, generates data for patent applications, and delivers services for the pharmaceutical industry in Taiwan. In this review article, a selection of conventional behavioral tasks and specific mouse behavioral tasks are described and introduced. The researchers also highlight how the choice of specific behavioral tasks during the experiment-planning phase should take into consideration a variety of factors, including their validity, reliability, sensitivity, utility, and specificity. Based upon the hypothesized hypofunction of the N-methyl-D-aspartate receptor (NMDAR)-mediated signaling pathways underlying common cognitive and social impairments in schizophrenia, three NMDAR-related compounds/drugs, D-serine, sarcosine, and D-cycloserine, are discussed in this article as examples for drug testing.

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Ching-Hsun Huang, Ju-Chun Pei, Da-Zhong Luo, Ching Chen, Yi-Wen Chen and Wen-Sung Lai. Assessing schizophrenia-relevant cognitive and social deficits in mice: a selection of mouse behavioral tasks and potential therapeutic compounds. Current Pharmaceutical Design, 20(32), 5139-5150, 2014 (doi: 10.2174/1381612819666140110122750).

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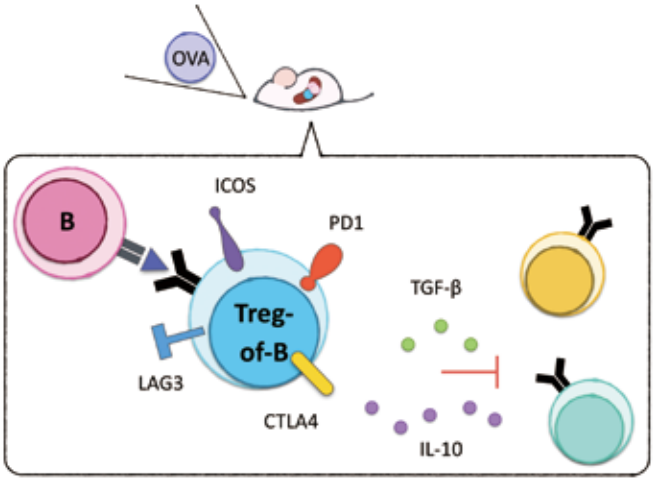
Single allergen-induced oral tolerance inhibits airway inflammation in conjugated allergen-immunized mice



The presentation of antigen derived from the oral route by B cells and the induction of Treg-of-B cells. Treg-of-B cells expressed regulatory molecules and cytokines to suppress antigen-specific and non-antigen-specific effector T cell responses.

The suppression of immune responses to proteins administered through oral routes is referred to as oral tolerance. The underlying mechanism of oral tolerance is sophisticated and has been studied for decades. Many patients develop allergic responses to house dust mites, which include more than 20 groups of allergens. The current study investigated the effect of oral tolerance induced through oral exposure to single proteins on animals with allergies to 2 or more proteins.

The mice were sensitized with conjugated proteins to mimic patients with allergies to multiple house dust mite allergens. We observed that single-protein-induced oral tolerance inhibited the immune responses to other allergens. This effect could be observed in animal models of allergic asthma and in vitro cell culture systems. These results demonstrated the existence of non-antigen-specific regulation of oral tolerance.

We further addressed the role of B-cell-induced regulatory T cells (also called Treg-of-B cells) in this model. B-cell-deficient mice showed defects in cytokine production after oral treatment, and we observed that antigen-presenting B cells modulated the proliferative responses of splenocytes to antigens ex vivo. Furthermore, we observed several similarities between oral-treated antigen-activated Treg cells and Treg-of-B cells, including marker expression, cytokine production, and suppressive function in vitro and in vivo. These data suggest that Treg-of-B cells play a role in the sophisticated mechanism of oral tolerance (Figure).

Few studies have reported the non-antigen-specific regulation of oral tolerance and the role of B-cell-induced Treg cells, and our findings provide information for the development of future therapeutic treatments for multiple allergen-induced allergic diseases.

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Chien-Hui Chien, Hsin-Hui Yu & Bor-Luen Chiang. Single allergen-induced oral tolerance inhibits airway inflammation in conjugated allergen immunized mice. J Allergy Clin Immunol. 136(4): 1110-3.e4 (2015). DOI: 10.1016/j.jaci.2015.04.018.

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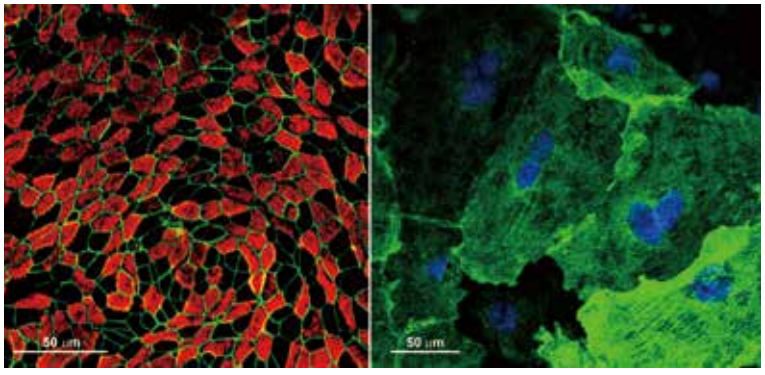
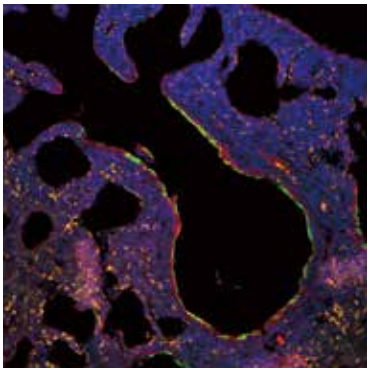
Lung-derived SSEA-1(+) stem/progenitor cells inhibit allergic airway inflammation in mice



SSEA-1+ pulmonary stem/progenitor cells differentiate into tracheal epithelial cell (left) and type I pneumocyte (right).



SSEA-1+ pulmonary stem/progenitor cells are localized in the bronchioles, terminal bronchioles, and the bronchoalveolar duct junction in the lungs of neonatal mice.

The research team of Professor Bor-Luen Chiang (Graduate Institute of Clinical Medicine) at National Taiwan University (NTU) has identified SSEA-1+ pulmonary stem/progenitor cells (PSCs) and demonstrated that these cells can inhibit allergic airway inflammation and reduce airway hyperresponsiveness (AHR) and lung damage, representing another breakthrough in research concerning allergic airway inflammation.

Asthma is a heterogeneous inflammatory disorder characterized by chronic airway inflammation, AHR, and excessive airway mucous production. The intensity of the pulmonary recruitment of eosinophils is strongly correlated with the severity of AHR. In most patients, asthma can only be symptomatically controlled through available medications. However, patients with inadequately controlled asthma often have limited therapeutic options and remain at a high risk of serious morbidity and mortality.

Chiang's team discovered that neonatal SSEA-1+ pulmonary cells are stem/progenitor cells capable of self-renewal and differentiation into pneumocytes and tracheal epithelial cells. These authors also found that neonatal SSEA-1+ PSCs could inhibit the production of two cytokines, thymic stromal lymphopoietin and eotaxin, in lung epithelial cells. Furthermore, adoptive transfer of SSEA-1+ PSCs into asthmatic mice suppressed eosinophil infiltration and airway inflammatory cytokine production, leading to significantly reduced AHR, inflammation and damage to the lungs.

This research has furthered the current understanding of the role of PSCs in the pathogenesis of allergic asthma and may provide new approaches for therapeutic management of allergic asthma in the future.

This study, entitled "Lung-derived SSEA-1+ stem/progenitor cells inhibit allergic airway inflammation in mice," was published and selected as the cover story in the April issue of Allergy 2015.

Reference

Chiao-rong Chiu, Thai-Yen Ling & Bor-Luen Chiang. Lung-derived SSEA-1(+) stem/progenitor cells inhibit allergic airway inflammation in mice. Allergy 4, 374 (2015). (Cover story of the issue) DOI: 10.1111/all.12567.

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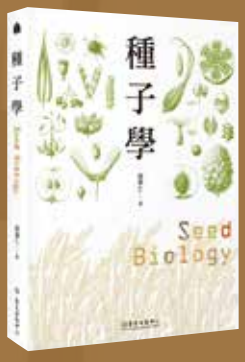

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