Leap into the Cutting-edge Terrain of Internationalization

After Adoption: Bridging a Way to Their Origins
DynaPho: A Phospho-Tool in Systems Biology
LANDSCAPE is published by National Taiwan University (NTU) and managed by the Division of Strategic Planning, Office of Research and Development. Content is prepared using information featured at the NTU Spotlight website* as well as original material specifically collected for this publication.

Editorial Team
Editor-in-Chief: Fang-Jen Scott Lee
Editorial Committee: Luisa Shu-Ying Chang, Chun-hsien Chen, Yi-Chun Wu, Chung-Jen Chen, Ming-Wen Chu
Editorial Staff: Chun-ju Hsiao, Pei-Chun Chen, Yi-Ping Lee, Yu-Yen Chang
Design Consultant: Chi-Chen Wu

Disclaimer and Intellectual Property Notice
All content and images used in the publication are owned or licensed by National Taiwan University; unauthorized use is prohibited. NTU’s logos are trademarks of National Taiwan University. Nothing contained herein shall be construed as conferring any license or right under any NTU intellectual property right, patent, copyright, or trademark. Information and links in the current issue of LANDSCAPE are verified when sent to press. The Office of Research and Development cannot be liable for information which is outdated or websites that are no longer valid. LANDSCAPE has made all available efforts to verify that all content in this issue is compiled with the full consent of copyright owners. LANDSCAPE would very much appreciate to hear from intellectual property owners who are not reasonably identified in this issue so that LANDSCAPE may make necessary corrections.

Please direct all inquiries on the reproduction or use of photos or imagery content for commercial use, future collaboration, questions or suggestions to ntucr@ntu.edu.tw or individual researchers as listed in the articles. All other reproduction is permitted if the source is acknowledged.

* Find out NTU Spotlight at http://www.ntu.edu.tw/spotlight/spotlight.html
All issues in PDF are available at http://ord.ntu.edu.tw/en/Landscape.aspx

© National Taiwan University 2018
Front cover image credits:
Earth © 588ku.com
Country flag icons designed and distributed free by Alain Jollat at antibakteriel.deviantart.com
Front cover designed by Chi-Chen Wu.
Back cover photo: Courtesy of Professor Hervé Capart.
Left Inner-page photo: Courtesy of Professor Yu-Pin Lin.
Right Inner-page designed by the Office of International Affairs, National Taiwan University.

Division of Strategic Planning
Office of Research and Development
National Taiwan University
1, Section 4, Roosevelt Road, Taipei 10617, Taiwan
+886 (0)2 33663262
ntucr@ntu.edu.tw

ISSN 2518-4326 (Print)
ISSN 2518-4326 (Online)
GPN 2010501304
In 2013, President Pan-Chyr Yang and Executive Vice President (EVP) Liang-Gee Chen envisioned the integration of university resources and the unification of research personnel for maximum global impact. Hence, the “Strategic Partnership Project” was conceived. The aim of the Project was to highlight the university’s top-notch research while strategically encouraging faculty and students to strengthen existing links with our key partners.

The Project launched in 2013 with the expected goal of 1+1>2. National Taiwan University (NTU) and its identified partner would collaborate to create new opportunities and exploit research synergies. Together, the collaborating universities aimed to improve in international reputation, increase their impact, and play a pivotal role in teaching and research globally. Together with the Deans from NTU’s 11 colleges, EVP Liang-Gee Chen studied each college’s alumni, research foci, and exchange students while also taking physical location and regional similarities into consideration in order to select the most promising partnerships. Every college then chose three potential universities as their short- and long-term research partners.

Five years after the initial launch, the Office of International Affairs has identified the University of Illinois at Urbana-Champaign (UIUC), Peking University, The University of Tokyo (UTokyo), Kyoto University, The University of Sydney (USYD), Hamburg University (UHH), and the University of Tsukuba as the strategic partners that NTU will collectively work with at the university level. Importantly, as Taiwan’s largest and most comprehensive university, NTU continues to carry out other research projects with a variety of institutions in addition to the abovementioned partners. Each college and department and individual researchers are still encouraged to conduct their own research and develop their own unique characteristics.

The Strategic Partnership Project has achieved outstanding results since its implementation in 2013. NTU and UIUC, UTokyo, Kyoto University, Peking University, and UHH have conducted more than 10 matchmaking conferences, connecting over 1,500 participants and producing hundreds of joint research publications. Though the model of collaboration may be different for each university, the research foci are always in line with the strengths of our renowned partners. Moreover, the research topics are all global issues of common concern. For example, under the “Smart Cities, Healthy Cities” framework, NTU and UIUC focused on community planning, food safety, public transportation, ageing, environmental health and other cross-disciplinary subjects. In addition to college and college matchmaking, NTU and Peking University have also piloted environment and ageing forums as the focal point of their collaboration. Similarly, after the initial matchmaking conferences between NTU and UTokyo and Kyoto University, several topics of interest have been identified, such as veterinary medicine, medical science, food safety, public health, agricultural technology, machinery, and marine science. In the case of Hamburg University, the emphasis was on the integration of each faculty’s individual research focus or the integration of 2-3 projects. This resulted in the formation of 11 research working groups in common areas of interest, such as digital humanities, biology, physics, arts and sinology. Each year, more than 50 faculty members and students are invited to participate in the University of Tsukuba’s Global Science Week (TGSW), an annual symposium that brings together internationally renowned researchers and aspiring young researchers and students to create a platform for transdisciplinary, trans-organizational and trans-border collaborations.
More recently, in 2017, NTU and the University of Sydney reached an agreement to establish a seed fund and subsidize a total of seven collaborative research projects over a period of three years – a solid plan to facilitate concrete research developments.

This issue of Landscape features three reports that came out of the Strategic Partnership Project. Prof. Yu-Wen Chen collaborated with USYD on cross-border adoption; Prof. C. Y. Chang wrote a paper on the relationship among the planning of urban areas, forests, and water resources and human health with his counterpart, Prof. William Sullivan from UIUC. Their collaboration represents a ten-year partnership between NTU and UIUC— from courtesy visits to joint publications, joint PhD supervision and a jointly appointed professorship, one of the most profound and concrete evidences of strategic partnership. Finally, the collaboration between Prof. Ru-Shi Liu and Kyoto University, which eventually expanded to include additional world-class university researchers, is a perfect example of the strategic partnership vision being taken to the next level, with its extension from bilateral to trilateral and multilateral collaboration.

Other reports in this issue may not be a direct product of the Project but have the potential to connect with the Project. For example, Prof. Yu-Bin Lin’s research on ecosystem protection planning and community environmental planning is highly aligned with the issues we have worked on with UIUC and Peking University. A paper by Prof. Shan-hui Hsu featured in this issue may not have derived from the Project, but Prof. Hsu is an active member of one research working groups collaborating with Hamburg University.

All the featured studies, whether directly engaged in the Project or not, reflect one of the emphases of NTU in the past ten years: international collaborations in advanced research. For example, Prof. Chia Wen Wu’s research on mesoporous materials is the fruitful outcome of the joint efforts of researchers from Taiwan, Japan, the United States, and Australia. Prof. Abby Ren from the Department of Geology engaged in coral reef research in the Pratas Islands (Dongsha Islands) with researchers from Taiwan and the United States. Prof. Hwei-Fang Tien worked with Italian scholars in her molecular genetics research on leukemia. Professor Chia-Lin Chung studied mycosis with scholars from Japan and the Philippines. The research findings of these scholars are examples of international collaboration. Such collaboration represents an academic trend of the future. Only through collaboration, close links, and collective trans-border, trans-disciplinary talent can we begin to solve pressing global problems.

With the efforts of NTU faculty and the support of the Strategic Partnership Project, we humbly present some of the results of the Project in this issue. However, our work is not finished. NTU aims to engage in further cross-disciplinary research and to leverage more research power and resources globally in order to achieve greater success and become a frontrunner in research on global issues, a contributor to humanity and the earth, and, as our former President Fu Sinian said, dedicate this university to the spirit of the universe.

Professor Luisa Chang, Ph.D.
Vice President for International Affairs
Feature: Leap into the Cutting-edge Terrain of Internationalization

04 Ten years of collaboration with the University of Illinois Urbana-Champaign
07 Coral record of an anthropogenic N perturbation in the remote open ocean
09 Glucose-sensitive self-healing hydrogel as sacrificial material for fabricating vascularized constructs
11 Molecular genetics of chronic lymphocytic leukemia in Taiwan
13 Self-assembly of conjugated rod-coil block copolymers for organic electronics
15 High-performance CsPb1-xSnxBr3 perovskite quantum dots for highly efficient light-emitting diodes
16 Deciphering brown root rot disease of trees: The comparative and population genomics landscape of Phellinus noxius
19 Positive in-plane magnetoresistance induced by nanodomain boundaries in graphene
20 Evidence-based international recommendations for difficult biliary access
21 Strategies for improving the functionality of zeolitic imidazolate frameworks
24 Systematically selecting conservation areas for habitat quality and multiple ecosystem services protection

People

26 Bridging a way to their origins – Introduction to the NTU-USYD collaborative project

Humanities and Social Sciences

29 Historical narratives in the pre-Qin and Han periods
31 Why should a guidebook, not a textbook, be written on Xunzi studies?
33 Climate change and societal risk

Life Sciences

35 ‘Micro’ organism, ‘macro’ problems
Studies of the MERS-CoV macro domain conducted by NTU structural biologists reveal a promising new therapeutic target.
36 Quadruplex formation enhanced by DNA methylation
Expression of the human telomerase reverse transcriptase gene is modulated by quadruplex formation in its first exon due to DNA methylation
39 An integrative tool for phosphoproteomics: a key in systems biology
40 Assembly of recombination-mediated DNA repair machinery

Natural Sciences and Engineering

42 Developmental changes in conceptual processing in children with autism
44 Contextual modulation of to-be-remembered information in visual working memory
45 Deep-sea corals and coral-bioeroding foraminifera in the South China Sea
47 Deep-sea ecosystem functions linked to biodiversity over the past 20,000 years
48 Quantum topological Hall effect in noncoplanar antiferromagnetic oxides
50 Light propagation in electrically driven liquid-core/liquid-cladding optical waveguides with electromicrofluidics
51 A fast-track characterization protocol of spin-orbit torque efficiencies

Medicine and Public Health

53 A novel mechanism of fine-tuning inflammatory responses
54 Snake venom is a key ingredient for developing anti-thrombotic agents
56 Influence of genetic variants on the response to lithium treatment in bipolar disorder

Business and Management

58 The R&D premium and takeover risk
Ten years of collaboration with the University of Illinois Urbana-Champaign

The “Built Environment and Health” session of the collaboration between the University of Illinois at Urbana-Champaign (UIUC) and National Taiwan University (NTU) represents a cooperative project between Professor William C. Sullivan from the Sustainability & Human Health Lab and Professor Chun-Yen Chang from the Healthy Landscape and Healthy People Lab, who have been cooperating closely for the past 10 years. The team has primarily focused on “landscape and human health” and collectively contributed a considerable number of publications on this subject. The team has worked to establish evidence-based landscape design via research to answer questions concerning the physiological, psychological, and social beneficial impacts of natural landscapes on humans. Moreover, they are also focused on developing a method of maintaining and sustaining an ecologically healthy landscape. In the past five years, the team has investigated the amounts of green areas, perception of green environments, biodiversity of green environments and different types of landscapes to understand how these variables affect human health. Lin, Tsai, Sullivan, Chang, and Chang (2014) have shown that street trees can enhance attention restorative ability, even without the participants’ awareness of them, and the group who paid attention observing street trees performed the best on attentional test.

If a person has a deeper connection with nature, he or she is more likely to experience an enhanced perceptual experience, and this experience may also improve the attention restorative ability (Tang, Sullivan and Chang, 2015). The characteristics of green environments may influence the benefits received from nature. Jiang, Chang, and Sullivan (2014) have shown that although a greater number of green areas is better, this relationship exhibits a curved line. This finding is popularly cited as a new understanding of the people-nature relationship. The biodiversity of an environment,

Figure 1. Examples of the experimental images (from top to bottom: urban, mountain, forest, and water; the left three images represent the environment, the right images show the baseline). (Tang et al., 2017)
one of the characteristics of environments, may positively and negatively influence human health. Chang, Sullivan, Lin, Su, and Chang (2016) used insects as an indicator to evaluate the biodiversity of urban green areas to examine the biofeedback response of participants, including electromyography (EMG), heart rate (HR) and blood volume pressure (BVP), and their results suggested that more and less biodiversity of green areas are influential factors on human physiological health indicators. Recently, the team has employed a functional magnetic resonance imaging (fMRI) instrument to examine brain activation when viewing landscapes and performing landscape design. Tang et al. (2017) used urban, mountain, forest, and river landscapes as stimuli, and participants viewed these images when in the fMRI instrument. The results indicated that focusing on the urban landscape compared with mountain and river landscapes required greater attention from the participants, with increased activation of brain areas controlling attentional and visual ability. In summary, this paper illustrates the topics assessed by the team regarding the beneficial health effects of nature.

To connect the members closely and substantially, the team developed collaboration patterns. For example, the exchange student program “International Study of Landscapes and Health Program” initiated in 2013 consisted of the exchange of two to five students from NTU to UIUC every fall semester, and to date, a total of twenty students have visited UIUC. Additionally, one undergraduate student and two PhD students have participated in the exchange with NTU to acquire foreign learning experience and experimental expertise. The exchange students have experienced cultural differences, and they have also learned to think and participate deeply in classes during their stay at UIUC. Moreover, Professor Sullivan is now an adjunct professor at NTU and Professor Chang also serves as an adjunct professor at UIUC, and they give lectures and instruct thesis students. The conference workshop is also worthy of mention. To draw attention to the professional field of landscape architecture in relation to human health, the team holds a conference workshop at the CELA Conference (Council of Educators in Landscape Architecture) or the EDRA Annual Conference (Environmental Design Research Association) annually. Members from both laboratories share research concepts and results in the workshop, and professors lead the discussion to encourage communication among the attendees.

Figure 2. Activated brain regions associated with “urban versus mountain”. The contrast was located in the cuneus, which is the basic visual processing brain area. (Tang et al., 2017)

Figure 3. Activated brain regions associated with “urban versus water”. The contrast areas were located in the cuneus, which is responsible for basic visual processing, and Brodmann area 31, which is responsible for adjusting attention (Tang et al., 2017).
In the future, the group will perform research to examine the relationship between landscape and human health and extend the research to environmental issues, such as environmental quality improvement of green infrastructures in urban areas, the resilience of urban landscapes, and disaster management. The collaboration between the Sustainability & Human Health Lab and the Healthy Landscape Healthy People Lab will continue. Thus, the network will grow over time, and as members graduate and establish new laboratories in other universities, the discoveries will be widely dispersed by the members.

References
6. The Landscape and Human Health Laboratory (LHHL). http://lhhl.illinois.edu/

Professor Chun-Yen Chang
Department of Horticulture and Landscape Architecture
cycmail@ntu.edu.tw
Coral record of an anthropogenic N perturbation in the remote open ocean

Like all organisms, marine phytoplankton require nitrogen to live and grow. Although the majority of the air we breathe is N₂, the nitrogen in the atmosphere is not available for use by most phytoplankton; certain bacteria and cyanobacteria that are capable of breaking the strong N–N triple bond represent exceptions. Before organisms can use nitrogen, N₂ gas must first be converted to a more chemically available form, such as ammonium, nitrate, or organic nitrogen. The inert nature of N₂ means that biologically available nitrogen is often in short supply in the ocean, limiting phytoplankton growth.

Within the last century, humans have become an important source of fixed nitrogen. In the early 20th century, Fritz Haber and Carl Bosch developed an industrial process to produce reactive nitrogen from atmospheric N₂ stores. The Haber-Bosch reaction soon became an important means of producing nitrogen-rich fertilizers. Meanwhile, the adoption of internal combustion engines and other industrial burning processes led to widespread releases of oxidized nitrogen (NOₓ) to the atmosphere. Through these activities, humans have more than doubled the amount of fixed nitrogen that is pumped into the biosphere every year. Most of this fixed nitrogen is deposited on land, but some escapes and travels long distances. Modeling studies suggest that the oceans far away from the continents are not immune to the impacts of humankind’s nitrogen fertilization experiment. However, little evidence exists to support this hypothesis. The signal of anthropogenic nitrogen deposition is diluted by ocean mixing, and its impact may also be counteracted by organisms capable of fixing atmospheric N₂.

Anthropogenic sources of nitrogen are often isotopically lighter than the nitrogen that circulates in ecosystems due to natural processes. Using ¹⁵N/¹⁴N stable isotope analysis, Ren et al. track the appearance of this isotopically light nitrogen in seasonally resolved coral from Dongsha atoll, a semi-closed circular coral reef atoll located 300 km from the nearest continental mass in the northern South China Sea. The authors find that the light-nitrogen signal increased just before 2000, coincident with massive increases in fossil fuel combustion in Asia but decades later than predicted by modeling work. The amplitude of change suggests that, by 2010, the atmospheric deposition of anthropogenic N represented approximately one-fifth of the annual input of N to the surface ocean in this region. This proportion appears to be at the lower end of other estimates.


This study provides two insights into human amplification of the nitrogen cycle in the South China Sea. 1) Fossil fuel use (including coal consumption and vehicle exhaust) may have been the major driver of increasing anthropogenic nitrogen deposition to the open ocean, and their effects may have been immediate. 2) The differences between the observations and previous modeling studies highlight gaps in our knowledge of the sources and pathways by which nitrogen deposition occurs in the open ocean.

This assessment of the extent to which humankind’s unintentional nitrogen release experiment has spread adds urgency to recent concerns about the multidimensional planetary boundaries that humanity is pressuring. It also highlights the urgency of monitoring the ocean environment over large areas and through time to better understand the extent of human influences on the open ocean. This study points out the tremendous potential value of a network of coral-based N isotope records from ocean islands and offshore reefs to deliver this information.


This study provides two insights into human amplification of the nitrogen cycle in the South China Sea. 1) Fossil fuel use (including coal consumption and vehicle exhaust) may have been the major driver of increasing anthropogenic nitrogen deposition to the open ocean, and their effects may have been immediate. 2) The differences between the observations and previous modeling studies highlight gaps in our knowledge of the sources and pathways by which nitrogen deposition occurs in the open ocean.

This assessment of the extent to which humankind’s unintentional nitrogen release experiment has spread adds urgency to recent concerns about the multidimensional planetary boundaries that humanity is pressuring. It also highlights the urgency of monitoring the ocean environment over large areas and through time to better understand the extent of human influences on the open ocean. This study points out the tremendous potential value of a network of coral-based N isotope records from ocean islands and offshore reefs to deliver this information.


Link to the full article: http://science.sciencemag.org/content/356/6339/749

The article has been highlighted in Science: http://science.sciencemag.org/content/356/6339/700
Figure 1. (A) Most of southeastern China was covered by a thick, grayish shroud of aerosol pollution in January 2002. The smog is so thick that it is difficult to see the surface in some regions of this scene, which was acquired on January 7, 2002. The city of Hong Kong is the large brown cluster of pixels toward the lower left-hand corner of the image (indicated by the faint black box). The island of Taiwan, due east of mainland China, is also blanketed by the smog. This true-color image was captured by the Moderate-resolution Imaging Spectroradiometer (MODIS) sensor onboard NASA's Terra satellite. This image is from NASA (https://visibleearth.nasa.gov/view.php?id=57534). Dongsha is the green circular ring located to the southwest of Taiwan in the South China Sea; it is marked with a red circle.

(B) The increase in the $^{14}$N signal observed in coral from Dongsha atoll occurred concurrently with the increase in fossil fuel combustion (including coal consumption and vehicle use) in China.

Reference

Assistant Professor
Haojia Abby Ren
Department of Geosciences
abbyren@ntu.edu.tw
A major challenge in tissue engineering is the lack of proper vascularization. Because host-capillary invasion upon the implantation of man-made tissues requires several weeks to achieve complete vascularization, insufficient nutrient and oxygen supply may lead to cell death in the core of the implant, causing problems in tissue integration. Therefore, building a vascular network within a tissue construct is a very important issue (Figure 1). Although various approaches have been used to build vascular networks in tissue-engineered constructs, some drawbacks remain. Recently, self-healing hydrogels, a class of smart materials, have drawn much attention in this context (Figure 2).

In this study, an injectable, glucose-sensitive self-healing hydrogel was employed as an easily removable sacrificial material to generate branched tubular channels within a construct. The hydrogel is composed mainly of reversibly crosslinked poly(ethylene glycol) diacrylate (PEGDA) and dithiothreitol (DTT) with borax as the glucose-sensitive motif (Figure 3). It can be rapidly removed by immersion in cell culture medium, and the stiffness can be fine-tuned by changing the concentrations of the polymers. The viscoelastic properties were measured by rheometry, and the oscillatory strain was used to indicate the self-healing capacity of the hydrogel. These characteristics can be employed to fabricate interconnected channels within scaffolds and develop a vascular network within a tissue-engineered construct (Figure 4).

Neural stem cells (NSCs) and vascular endothelial cells (ECs) were used to observe the morphology and proliferation of cells in the vascularized construct. In the construct, vascular ECs significantly proliferated, and a precapillary-like structure in the bulk gel near the channel started to form. In addition, ECs in the construct expressed more angiogenesis-associated genes and chemokines/receptors, and NSCs in the construct expressed higher levels of a mature neuron marker gene (Map2), an angiogenic factor (VEGF gene), and chemokine receptors. Cell morphology was observed by microscopy after 14 days. ECs previously seeded inside the channels migrated from the lumen wall of the channels into the bulk gel and aligned to form capillary-like structures in the construct. The dispersed NSCs in the non-sacrificial hydrogel proliferated and formed neurosphere-like structures. These results suggest that co-culturing ECs and NSCs in such a pre-designed construct may facilitate EC angiogenesis (Figure 5).

This research was published in Biomaterials in 2017 (133: 20–28) and was conducted by Dr. Shan-hui Hsu, a distinguished professor at the Institute of Polymer Science and Engineering at NTU, Dr. Yen Wei, a professor at the Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Dr. Patrick Theato, a professor at the Institute for Technical and Macromolecular Chemistry, University of Hamburg, Hamburg, Germany, Dr. Ting-Chen Tseng and Dr. Fu-Yu Hsieh, formerly a doctoral student and currently a postdoctoral researcher in Hsu’s lab. This word is a good example of international collaboration on innovative research. Professor Wei was the first to report the self-healing character of the chitosan/PEG hydrogel, while Professor Theato was the first to report the self-healing character of the PEGDA/DTT/borax mixture.

Reference

Professor Shan-hui Hsu
Institute of Polymer Science and Engineering
shhsu@ntu.edu.tw
Figure 1. Schematic diagram of substance (e.g., nutrients and oxygen) exchange between vascular networks and tissues.

Figure 2. The property of self-healing hydrogels.

Figure 3. Synthesis scheme for preparation of glucose-sensitive self-healing hydrogel.

Figure 4. The glucose-sensitive self-healing hydrogel is embedded in another hydrogel (non-sacrificial) and then immersed in culture medium. The self-healing hydrogel is solubilized in culture medium, and a tunnel forms inside the construct.

Figure 5. Graphical abstract of this study showing that when NSCs and ECs are encapsulated in the vascularized construct, ECs line the tube during the early stage and then migrate to form precapillaries. (Red fluorescence: ECs. Green fluorescence: NSCs.)
Molecular genetics of chronic lymphocytic leukemia in Taiwan: clinical and pathogenetic implications

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in the Western world. CLL belongs to the indolent lymphoma category, but its clinical course varies widely. During the preceding three decades, many clinical and molecular features have been identified as predictors of outcome or of response to therapy. These molecular and clinical markers of CLL have greatly improved our understanding of the biology of this disease and contributed to the optimization of individual patients’ management options. CLL is much less prevalent in Asia; it is viewed as a “Western disease”, and most knowledge about CLL is derived from studies in Western populations. This knowledge gap has become particularly significant since our prior studies have shown less favorable outcomes of CLL in Taiwan than those in the West. Thus, any differences in biological characteristics that may underlie this disparity in the prognosis of CLL in Asian populations relative to Western populations would be of great interest and value.

In collaboration with Professor Paolo Ghia at Università Vita-Salute San Raffaele and Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Scientifico San Raffaele, Milano, Italy, as well as Professor Liang-In Lin at the Department of Clinical Laboratory Science and Medical Technology, College of Medicine, National Taiwan University, Professor Hwei-Fang Tien and Dr. Shang-Ju Wu conducted the current study, which sought to characterize and validate clinical implications of CLL immunogenetic and genetic features in a cohort of Taiwanese CLL patients, to highlight any potential geographical differences that may underlie the aforementioned outcome disparity. We found that the IgHV gene repertoire in this cohort was biased and distinct from that observed in Western cohorts, with the most common IgHV genes being IgHV3-23, IgHV3-7, and IgHV3-48 (Figure 1A and 1B).

Figure 1. (A) Frequencies of IgHV subgroups and somatic hypermutation statuses in Taiwanese CLL patients. (B) Comparison of frequencies of IgHV gene usage in Western and Taiwanese CLL patients.
The observed differences in \(IgHV\) properties suggest that different pathogenetic factors are involved in the development of CLL. With respect to the mutational status of the \(IgHV\) gene, 63.8% of the patients carried mutated rearrangements, whereas 22.4% of the patients were assigned to stereotyped subsets (with 6.9% and 15.5% of the patients assigned to major and minor subsets, respectively). The frequencies of \(NOTCH1\), \(SF3B1\), \(BIRC3\) and \(MYD88\) mutations were 9.6%, 7.2%, 1.2%, and 2.4%, respectively; however, the frequency of \(TP53\) mutation was significantly higher (20.5%) in our cohort than that in Western cohorts (Figure 2A and 2B). This high \(TP53\) mutation frequency could partially explain the dismal outcomes of patients with CLL in Taiwan.

Figure 2. (A) Gene mutation and cytogenetic aberrancy statuses; each column represents an untreated CLL case in the current study. (B) Frequencies of common gene mutations in Taiwanese and Western CLL patients.

The current study revealed immunogenetic and genetic features of Taiwanese CLL patients and the clinical implications of these features and highlighted geographical differences that may underlie the outcome disparity between Taiwanese and Western CLL patients. This knowledge could lead to the refinement of management strategies for Taiwanese CLL patients.
Self-assembly of conjugated rod-coil block copolymers for organic electronics

The field of organic electronics has enjoyed increasing interest over the past decade. Organic light-emitting diodes, field-effect transistors and solar cells have a promising future, with some products already commercially available. Polymers typically offer good solution processability, paving the way for potential low-cost and large-area applications. However, the morphology always plays the decisive role in such devices since it has a large effect on the charge-transport properties.

Block copolymers are covalently linked polymers. The interconnectivity of the polymers restricts the formation of large domains, leading to so-called microphase separation. The crystallinity of one or both of the polymer blocks has a significant contribution to the enthalpy of the material system, thereby influencing the microphase separation. Rod-coil block copolymers show a further complexity because the conformational entropy is strongly influenced by the stiffer chain topology and because of the specific interactions between the conjugated moieties. The term “coil” describes the amorphous polymer segments, while the term “rod” is used for stiffer conjugated polymer segments.

A joint research study led by Professor Wen-Chang Chen in the Department of Chemical Engineering at NTU and Professor Toshifumi Satoh in the Graduate School of Chemical Sciences and Engineering of Hokkaido University designed a series of rod-coil copolymers for different kinds of organic electronic device applications. For example, main-chain conjugated, electron-donating polyfluorene (PF) rods and pendent electron-withdrawing isoindigo (Piso) coils were synthesized for resistor memories [1]. Self-assembled fibrillar nanostructures and effective charge-transport channels were formed in the polymer thin films by thermal annealing, leading to stable resistance switching behavior for memory device applications. The enhanced conjugated PF conducting channels led to stable resistance switching behavior, exhibiting volatile static random-access memory (SRAM) and nonvolatile write-once-read-many-times (WORM) memory. The results indicate that stable digital information storage could be achieved, and the charge storage volatility could be easily manipulated by tuning the PF/Piso ratio. More importantly, the memory cells were integrated on a poly(dimethylsiloxane) (PDMS) substrate to make the devices stretchable.

Moreover, poly(3-hexylthiophene) (P3HT) rod segments can potentially be coupled with coil segments to produce P3HT-coil block copolymers for field-effect transistor [2] and transistor-type memory [3] applications. Poly(3-hexylthiophene)-block-poly(butyl acrylate) (P3HT-b-PBA) thin films combined the good semiconducting properties of P3HT and the mechanical endurance of PBA to fabricate a stretchable transistor. Incorporating the low glass-transition temperature PBA block enhances the ductility of the polymer film while maintaining good charge-transport ability under 100% strain or after 100 cycles of strain due to the self-assembled fibrillar-like nanostructures and edge-on orientation of the P3HT-b-PBA film. Our newly synthesized P3HT-b-pendent Piso donor-acceptor rod-coil copolymers show dual electrical functionalities. Such block copolymer film is then introduced as both a charge-transport and charge-storage layer in an OFET memory device configuration. A p-type channel can be formed, and the memory window can be tuned by the block length of the Piso coil. From our findings, we demonstrate strategies for the synthesis of rod-coil block copolymers containing multiple electronically interesting components as well as control over their self-assembly.
References


Professor and Dean
Wen-Chang Chen
Department of Chemical Engineering, College of Engineering
chenwc@ntu.edu.tw
High-performance CsPb$_{1-x}$Sn$_x$Br$_3$ perovskite quantum dots for highly efficient light-emitting diodes

All inorganic CsPbBr$_3$ perovskite quantum dots (QDs) have attracted considerable interest because of their high photoluminescence, tunable and narrow emission wavelength, and facile synthesis. Given these advantages, all inorganic CsPbBr$_3$ perovskite QDs can be used in solar cells, lasing, light-emitting diodes (LEDs) and bioimaging. However, the toxicity of Pb$^{2+}$ has a negative impact on the environment. Hence, the total or partial replacement of Pb$^{2+}$ is necessary. At present, the most suitable substitute elements are the less toxic Sn(II), Sn(IV), Bi(III) and Mn(II) ions. Thus, partially Sn-substituted perovskite QDs were prepared in a colloidal solution. After a long reaction time, the Sn(IV) ions reached the maximum substitution ratio, and the valence state of the Sn ions was confirmed by X-ray absorption near-edge spectroscopy (XANES). The Sn K-edge XANES spectra of the CsPb$_{1-x}$SnBr$_3$ QDs indicated that the absorption edge energies of all the analyzed samples were the same and fit the Sn(IV) ion standard curve. These results are attributed to the easy oxidation of Sn(II) ions during the synthesis of QDs at high temperature. According to the inert pair effect, the stable valence state of Sn is Sn(IV). The absolute photoluminescence quantum yield (PLQY) of CsPb$_{1-x}$Sn$_x$Br$_3$ QDs substituted with Sn(IV) increased from 45% to 83%, where the best substitution ratio was $x = 0.33$. Based on femtosecond transient-absorption (TA), time-resolved photoluminescence (TRPL), and single-dot spectroscopies, we concluded that the observed PLQY enhancement was due to the reduction of trion formation in the perovskite QDs. These highly luminescent CsPb$_{0.67}$Sn$_{0.33}$Br$_3$ QDs that exhibit an emission wavelength of 517 nm have potential for application as emitters for electroluminescent displays. Thus, CsPb$_{1-x}$Sn$_x$Br$_3$-based quantum dot LEDs (QLEDs) with the structure ITO/PEDOT:PSS/TFB/PQDs/TPBi/LiF/Al were fabricated.

The optimized device exhibited a luminescence of 12,500 cd/m$^2$, a current efficiency (CE) of 11.63 cd/A, an external quantum efficiency (EQE) of 4.13%, a power efficiency (PE) of 6.76 lm/w, and a low turn-on voltage of 3.6 V.

In summary, we demonstrate the hot-injection synthesis of...
CsPb1-xSnxBr3 perovskite QDs with Sn(IV) substitution. Sn(IV) doping effectively suppresses the formation of trions, as revealed by single-dot, TRPL, and TA spectroscopies. The best perovskite QLED device displays a luminescence of 12,500 cd/m², a CE of 11.63 cd/A, an EQE of 4.13%, a PE 6.76 lm/w, and a low turn-on voltage of 3.6 V, which are the highest values reported among all Sn-based perovskite QLEDs.

Reference

Glossaries
Exciton: the combination of an electron and a positive hole, which is free to move through a nonmetallic crystal as a unit.
Trion: a localized excitation which consists of three charged quasiparticles. A negative trion consists of two electrons and one hole and a positive trion consist of two holes and one electron.
PEDOT:PSS (poly(3,4-ethylenedioxythiophene) polystyrene sulfonate): a polymer mixture of two ionomers that functions as a hole injection layer in QLEDs.
TFB (poly[(9,9-dioctylfluorenyl-2,7-diyl)-co-(4,4′-(N-(4-sec-butylphenyl)diphenylamine))]): a polymer that functions as a hole transport layer in QLEDs.
TPBi (2,2′,2″-(1,3,5-benzinetriyl)-tris(1-phenyl-1-H-benzimidazole)): a kind of electron transport layer in QLEDs.

Professor Ru-Shi Liu
Department of Chemistry
rsliu@ntu.edu.tw

Deciphering brown root rot disease of trees
The comparative and population genomics landscape of Phellinus noxius

Under most circumstances, fungi coexist with trees or act as saprotrophs responsible for carbon and nitrogen cycling in forest systems. The order Hymenochaetales is dominated by wood decay fungi and belongs to Agaricomycetes in Basidiomycota. Most species in this order are saprotrophic or weakly pathogenic, but a few of these species exhibit strong pathogenicity. In various parts of the world, there has been an emergence of tree disease outbreaks, including brown root rot caused by Phellinus noxius and laminated root rot caused by Phellinus sulphurescens. Despite the ecological importance of these fungi and the impact of the diseases that they cause, little is known about their evolution and transmission patterns.

During the last 20 years, brown root rot disease has become a serious threat to a variety of agricultural, ornamental, landscape, and forest trees in Taiwan; the Ryukyu Islands and the Ogasawara Islands of Japan; Hong Kong; and Macao. The pathogen P. noxius has an extremely wide host range that spans more than 200 broad-leaved and coniferous tree species (in at least 59 families), such as longan, litchi, camphor, ban-yan, and pine trees. The corresponding disease is widespread in tropical and subtropical areas in Southeast Asia, East Asia, Oceania, Africa, Central America and the Caribbean. This geographical distribution appears to be related to the growth temperature range of P. noxius, which is
10-12°C to 36°C, with optimum growth at 30°C. Although *P. noxius* is recognized as an emerging destructive pathogen that causes tree death, its genome, evolution and global population genetics are poorly understood.

In a joint international effort led by Dr. Isheng J. Tsai from the Biodiversity Research Center, Academia Sinica, and Dr. Chia-Lin Chung from the Department of Plant Pathology and Microbiology of National Taiwan University (NTU), who collaborated with the Japan Forestry and Forest Products Research Institute, University of Miyazaki, Japan, as well as Taiwan Agricultural Research Institute and NTU’s Department of Bio-industrial Mechatronics Engineering, a reference genome of *P. noxius* and high-quality assemblies of three closely related Hymenochaetales species (the wood-decomposing fungus *P. lamaensis*, the laminated root rot fungus *P. sulphurascens* and the trunk pathogen *Porodaealea pini*) were released.

Long-read sequencing was used to sequence the ~31 Mb genome of *P. noxius* to a high level of completion; notably, telomere-to-telomere chromosome sequences were obtained. Comparative genomics analyses of Hymenochaetales genomes identified many gene families of lignin-degrading enzymes, reflecting the examined organisms’ capacity to act as white rot fungi. The *P. noxius* genome contained highly expanded 1,3-beta-glucan synthase genes, which may account for its fast-growing nature. A total of 4.23% of the *P. noxius* proteome was annotated as carbohydrate-active enzymes (CAZymes); this percentage was higher than those observed for other Hymenochaetales species. The comprehensive repertoire of CAZymes encoded in the *P. noxius* genome suggests this fungus’s capability to infect a wide range of hosts.

To further understand the biology and regional dissemination of *P. noxius*, the research team sequenced the genomes of 60 isolates originating from diseased trees across Taiwan and offshore Japanese islands from 2007-2014. Population genomics analyses suggested that *P. noxius* is a hypervariable species for which both monokaryotic and heterokaryotic states of mycelia are prevalent in nature. Investigations into mating type loci and genome-wide heterozygosity indicated that this organism’s genetic hyperdiversity can be attributed to its bipolar heterothallic reproductive system and heterokaryotic nature. Evidence from whole-genome sequencing and simple sequence repeat (SSR) markers suggested that *P. noxius* may disperse over short distances via root-to-root contact between host plants and that genetically variable basidiospores are likely responsible for long-distance dispersal. Moreover, long-distance dispersal via the transport of infected plants/stumps or colonized wood debris by human activities cannot be excluded. In addition, it was revealed that *P. noxius* from the Ryukyu Islands may have originated in Taiwan and that *P. noxius* in the Ogasawara Islands (located 1,210 km from the Ryukyu Islands) may have been derived from a genetically distinct gene pool and could have undergone divergent evolution. The different evolutionary histories of these two *P. noxius* populations could reflect different times of introduction, different environments, and human interference in the Taiwan-Ryukyu and Ogasawara regions.

The genetic hyperdiversity of *P. noxius* suggests that this pathogen may be highly adaptable to different environments and stresses. Much more attention must be devoted to how global warming and the increasing frequency of extreme weather events will exacerbate disease severity and allow a fast-growing pathogen such as *P. noxius* to colonize warm temperate zones.

**References**


**Associate Professor**

Chia-Lin Chung  
Department of Plant Pathology and Microbiology  
clchung@ntu.edu.tw

Dr. Isheng J. Tsai  
Biodiversity Research Center, Academia Sinica  
ijtsai@gate.sinica.edu.tw
Figure 1. Life stages of *P. noxius* and a comparative genomic analysis of Hymenochaetales species. (a) *P. noxius* mainly infects the roots of the host tree, with infections sometimes accompanied by gradual expansion of the mycelial mat to the basal stem. The mycelial mat has a young, cream-colored leading front and an aged brown section. (b) In trees in an advanced stage of decay, the hyphae form a network of brown zone lines that permeate the soft, white wood tissue. (c, d) Basidiocarps are perennial and can be resupinate (c) or grow into a sessile, bracket-like conk with a broad basal attachment (d). The distinctive grayish-brown surface is the hymenial layer with irregular polygonal pores that contains four-spored basidia and ellipsoid and hyaline basidiospores but no hymenial setae. (e) The phylogeny of the four *Phellinus* species sequenced in this study. *P. noxius* and *P. lamaensis* are more closely related and have smaller genomes (~31 Mb); *P. pini* and *Fomitiporia mediterranea* have larger genomes (53-63 Mb).

Figure 2. Map of Taiwan and offshore Japanese islands that shows the origins of the 60 *P. noxius* isolates sampled from 2007-2014. *P. noxius* isolates from Taiwan and the Ryukyu Islands belong to the same lineage, whereas isolates from the Ogasawara Islands (1,210 km apart) are genetically distinct.
Positive in-plane magnetoresistance induced by nanodomain boundaries in graphene

Graphene supports long spin lifetimes and long diffusion lengths, making it promising for spintronics. However, rendering graphene magnetic remains a fundamental challenge. Among the different types of graphene, graphene with zig-zag edges and ripples are the most promising candidates, as zig-zag edges are predicted to host spin-polarized electronic states and ripples can induce spin–orbit coupling (SOC).

We investigated the magnetoresistance (MR) of graphene grown on SiC/Si(001) wafers, in which inherent nanodomain boundaries (NBs) sandwich zig-zag structures between adjacent ripples of large curvature (Fig 1b). Localized states at the NBs result in an unprecedented positive in-plane MR (Fig 1c). Our work may offer an exciting way to add the spin degree of freedom to graphene.

Figure 1d shows the calculated charge density distribution under various bias voltages. An obvious charge density accumulation occurs at the NB, and when the bias is increased to a value of 0.5 V, the charge density begins to spread across to the NB. The charge density is greater along the NB than in the pristine graphene, clearly demonstrating the 1D transport properties of the NBs at low bias voltages. Furthermore, the large curvature at the ripples of the graphene can result in SOC. To investigate the spin-dependent transport across the NBs with weak SOC, we calculated the spin density distribution under a bias voltage of 0.4 V in Fig. 1e. Clearly, only electrons with a particular spin can cross the NBs under a bias voltage of 0.4 V, indicating that NBs with ripples can work as spin filters and that the SOC at ripples causes spin-dependent energy splitting.

Moreover, when an in-plane magnetic field is applied perpendicular to the NBs, fewer electrons can cross the NBs, implying a positive MR, which is consistent with the MR calculation. We also investigated the length variation in the NB, disorder within a single NB, and orientation of the magnetic field. The relative strengths of the spin filter and confinement effects are shown to be only marginally influenced, and the fundamental phenomenon is still observed.

The NBs with ripples are shown to have the potential to work as a spin filter and can result in a positive MR at low temperature. Moreover, our work suggests that graphene with NBs has localized states and large spin-orbit interaction at the ripples. The confinement of electrons of a particular spin direction from 2D to 1D NBs by the Zeeman effect is responsible for the positive MR observed at high temperatures.

Figure 1. MR and spin filtering effect of graphene containing a single NB. (a) Schematic drawing of the model used. (b) Schematic drawing of the structure of an NB. (c) MR of graphene containing a single NB calculated with an in-plane magnetic field. (d) Calculated charge distribution at different bias voltages. (e) Calculated spin density distribution perpendicular to graphene plane under a bias voltage of 0.4 V to demonstrate the spin-filtering effect due to the localized state of an NB and SOC of 0.1 meV at ripples. The sign indicates the orientation of the spins. (f) Schematic electrical transport and spin-filtering effect due to localized state of NBs and SOC at ripples.
Evidence-based international recommendations for difficult biliary access
A must-read for endoscopists

Endoscopic retrograde cholangiopancreatography (ERCP) is the preferred treatment for bile duct stones and plays an important role in the management of various diseases of the biliary duct and pancreas. The first step in ERCP is advancement of the endoscope to the bile duct opening in the duodenum followed by entry into the bile duct; further endoscopic therapy is then administered. Difficulty achieving biliary access is a commonly encountered challenge, with an estimated incidence of 11% in patients with normal anatomy. In patients with altered anatomy of the gastrointestinal tract due to previous surgeries, the incidence of difficult biliary access is even higher, and special instruments and techniques are often needed. Various approaches are currently used to manage difficult biliary access, including advanced endoscopic techniques and methods involving specialized endoscopic equipment. However, there is little consensus regarding the optimal approach for each condition that leads to difficult biliary access.

To provide endoscopists with evidence-based recommendations for managing difficult biliary access, researchers from the Department of Internal Medicine of National Taiwan University Hospital organized a panel of leading experts from different countries to review available evidence from existing research and generate consensus recommendations using the modified Delphi method. A total of 13 statements were generated and presented along with corresponding supporting evidence as well as grades for this evidence and the recommendations.

This consensus provides a standardized definition of difficult biliary access as the inability to achieve access via standard ERCP techniques within 10 minutes or up to 5 attempts or failure to access the bile duct opening. An increased risk of post-ERCP pancreatitis with difficult biliary access and the need to implement measures to reduce the risk of pancreatitis are highlighted.

For patients with normal anatomy, available salvage techniques and the experts’ preferences in various clinical scenarios are discussed in detail, with consideration of success and complication rates. For patients with surgically altered anatomy, the utility of device-assisted enteroscopy and the emerging technique of endoscopic ultrasound-guided biliary access are discussed and compared.
Zeolitic imidazole frameworks (ZIFs), a subclass of metal-organic frameworks (MOFs) built with tetrahedral metal ions and imidazolates, offer permanent porosity and high thermal and chemical stability. While ZIFs possess some attractive physical and chemical properties, it remains important to enhance their functionality for practical applications. Here, we provide an overview of the extensive strategies that have been developed to improve the functionality of ZIFs, including linker modifications and functional ZIF hybridization via the encapsulation of guest species (e.g., metal and metal oxide NPs and biomolecules).

This consensus provides the first state-of-the-art, evidence-based framework for this challenge that endoscopists encounter in daily practice. Because it may improve patient care and safety, this consensus has been recommended by various journals in medicine/gastroenterology fields as a must-read for endoscopists.

**Reference**


Professor Hsiu-Po Wang
Department of Internal Medicine
wanghp@ntu.edu.tw

**Strategies for improving the functionality of zeolitic imidazolate frameworks**

Tailoring nanoarchitectures for functional applications
Encapsulation of biomolecules in ZIFs

The coupling of MOFs with enzymes either by physical adsorption or covalent binding of the enzyme molecules to the presynthesized host can impart molecularly specific functions to the enzymes.[1] In the case of using a MOF with microporous windows for encapsulating an enzyme with a larger dimension than its normal window or cage size, the enzyme has to be encapsulated by constructing the MOF in the presence of the enzyme, otherwise change in the conformation of the protein can allow it to travel through the nanopores. However, such a phenomenon is not yet known for ZIF materials. To date, there are two main methods that have been used to encapsulate enzymes in MOFs, namely, de novo encapsulation (including coprecipitation and biomineralization) and post-synthetic encapsulations (mainly used for channel-type and cage-type MOFs).

Highly functional ZIF-enzyme composites have been synthesized by employing a de novo approach using ZIFs with a pore size smaller than the size of the mixture of two or more enzymes. For instance, ZIF-90, with a pore window of ~0.35 nm, could be used to selectively encapsulate the catalase enzyme, a hydrogen peroxidase, with an average size of ~10 nm (Figure 2). This unique concept of size-selective encapsulation has been shown to increase the resistance of embedded enzymes to inhibitors or proteases, such as proteinase K.[2] The true embedding of the enzyme, catalase in this case, can be demonstrated by comparing its gel-electrophoresis behavior with that of a fluorescent-labeled catalase. Despite the lower rate of H$_2$O$_2$ degradation of CAT@ZIF-90 in the presence of protease because of the encapsulation of the enzyme in ZIF-90 and due to the mass-transport limitations or nonoptimized interfaces between ZIF-90 and catalase, the de novo aqueous embedding method can lead to a functional composite with more active enzyme than an embedding method that uses conventional ZIF-90 synthesis in ethanol, an agent that may denature catalase or other embedded enzymes. This type of size-selective encapsulation to protect an enzyme from digestion or inhibition may offer a novel tool to immobilize and impart new functions to biomolecules (DNA, RNA, proteins) for biomedical applications.

Figure 1. An illustration showing the functionality of ZIF-derived materials.

Figure 2. Schematic illustration of the selective encapsulation of catalase in ZIF-90 with high functional activity for hydrogen peroxide decomposition.
Hybridization of ZIFs with polymeric matrix

Even though ZIF particles have shown promising properties for gas and liquid separations, they are often present as dry powders, which are unfavorable for industrial-scale applications. To improve the practical applications of ZIF for gas and liquid separations, they can be incorporated as additives into polymeric matrices to form mixed matrix membranes (MMMs). Despite the advantages exhibited by ZIF-8, there are several challenges for synthesizing ZIF-8-based MMMs, including the following: (i) achieving good ZIF-8 particle dispersion in the polymer matrix without significant agglomeration and (ii) avoiding the formation of nonselective interfacial voids between the polymer and ZIF-8 particles. To overcome these issues, we have recently developed a drying-free, water-based process for the fabrication of a ZIF-8/polyvinyl alcohol (PVA) MMM with outstanding performance for water/ethanol separation.[3] The proposed water-phase synthesis is highly advantageous, as water molecules can ensure the good distribution of ZIF-8 nanoparticles (NPs) in the PVA matrix. In contrast to conventional methods that involve the drying and re-dispersion of ZIF-8 and result in cracking and phase-separated MMMs (Path A in Figure 3), the new approach does not require a drying step and generates a transparent, crack-free MMM with well-dispersed ZIF-8 NPs (Path B in Figure 3). When employed for the dehydration of an ethanol/water mixture (90:10 w/w) at 25 °C, the PVA/ZIF-8 MMM with 39 wt% ZIF-8 loading showed a significantly larger permeability flux and separation factor values of 2.07 x 10⁶ Barrer and 4725, respectively, compared with a pure PVA membrane (0.75 x 10⁶ Barrer and 543, respectively). Furthermore, the separation performance of these PVA/ZIF-8 MMMs exceeded that of many previous ZIF-based MMMs. The significant enhancement of the separation performance was attributed to the large increase in the fractional free volume and the absence of interfacial voids as a result of the good adherence of PVA to ZIF-8.

![Figure 3. Schematic illustration of the preparation of PVA/ZIF-8 MMMs from ZIF-8 suspensions with and without drying.](image-url)

References

Professor Kevin C.-W. Wu
Department of Chemical Engineering
kevinwu@ntu.edu.tw
Systematically selecting conservation areas for habitat quality and multiple ecosystem services protection

Conservation areas generally consist of natural resources that must be sustained and preserved, such as habitats, species, ecosystems, and the services they provide. Accordingly, the natural environment of the conservation area is preserved and protected by policies that restrict certain human activities.

Many academic studies have focused on the provisioning capacity of natural resources, but the importance and provisioning capacity of ecosystem services have often been neglected. Along with the increasing awareness of how human activities exploit natural capital, conservationists and scientists have raised a call to establish, implement, and execute appropriate policies that incorporate ecosystem services into conservation strategies for real-world decision making since habitat quality and ecosystem supply are essential to identifying areas that require conservation measures. Although our scientific understanding of individual ecosystem services is becoming increasingly comprehensive, the inter-relationship and spatial patterns among multiple ecosystem services are scarcely discussed. However, appropriate policies that result in effective conservation and maintain ecosystem service benefits are necessary for human wellbeing.

Professor Yu-Pin Lin from the Department of Bioenvironmental Systems Engineering at National Taiwan University and his research team proposed a novel systematic approach to synchronously consider both the spatial connectivity of selected conservation areas and a dynamic system of multiple ecosystem services in balance. Habitat quality autocorrelations, multiple ecosystem services, and spatial patterns were considered when identifying ecosystem services conservation areas that are the most ‘efficient.’

The Wutu watershed located east of Taipei City was selected as the study area and is covered primarily by forest (83% of the total area). To estimate the habitat quality and ecosystem services, land use and climate data were used as inputs, and habitat quality and ecosystem services (HQ-ESs) were selected for quantification with the InVEST (Integrated Valuation of Ecosystem Services and Tradeoffs) tool, including carbon storage, biodiversity (using habitat quality as a proxy), nitrogen retention, phosphorous retention, soil retention, and water yield. From this information, quantified ecosystem services were derived, and a sensitivity analysis of nutrient retention was conducted. The Local Indicators of Spatial Association (LISA)-Zonation R-software package was developed by the research team. R (https://www.r-project.org/), a free software source code form, and QGIS 2.2.0

![Figure 1. Study flow chart (modified from Lin et al., 2017)](image)
Figure 2. Potential conservation areas in Scenario 2 identified using Zonation with different representation targets: (a) 10%, (b) 20%, and (c) 30% (modified from Lin et al., 2017)

Figure 3. Proportions of ecosystem services in the reserve areas under Scenarios 1, 2 and 3 with different representation targets: (a) 10%, (b) 20%, and (c) 30% (modified from Lin et al., 2017)

Scenarios 2 and 3 identified more efficient conservation areas by selecting high proportions of forest reserve sites as the conservation area, while Scenario 1 identified conservation areas scattered over the entire study area and therefore comprised lower proportions of reserve sites. Although no single conservation strategy can be applied to all regions or all situations, the findings suggest that conservation area selection efficiency can be increased. Furthermore, we can better protect biodiversity and multiple ecosystem services when the total habitat area, habitat quality, connectivity, and spatial patterns are included in the conservation area evaluation process.

Reference

Professor Yu-Pin Lin
Department of Bioenvironmental Systems Engineering
yplin@ntu.edu.tw
Intercountry adoptions have been justified as being in the best interests of children who cannot receive suitable care in their country of origin. However, the rights and wellbeing of these children are a point of concern. Australia and Taiwan are indelibly linked by the adoption of Taiwanese-born children by Australian families through intercountry adoption. From 2011 to 2014, Taiwan sent the most infants to Australia and was the leading sending country for Australian intercountry adoptions (Australian Institute of Health and Welfare [AIHW], 2016). However, post-adoption services in Taiwan remain unclear. Little is known regarding the new lives of Taiwanese adoptees in Australia. On the other hand, with an increase in the number of grown adoptees searching for their birth families, it is important to create a way for adoptees to connect with psychologically relevant family members, to help adoptees know who they are and where they are from.

Thanks to a Partnership Collaboration Award from the University of Sydney (USYD) and National Taiwan University (NTU), Professor Yu-Wen Chen from the Department of Social Work at NTU and Director Amy Conley Wright from the Institute of Open Adoption Studies at USYD School of Education and Social Work started their collaborative project on the issues related to intercountry adoptions. This research partnership leverages a key research strength for the School of Education and Social Work at USYD: the newly established Institute of Open Adoption Studies. Dr. Wright serves as the Director of this Institute, which brings expertise in adoption, networks among governmental and nongovernmental organizations facilitating adoption, and visibility through its website and distribution lists to disseminate findings to a wide audience. Dr. Chen’s research background is also an excellent match, focusing on the welfare and rights of disadvantaged children and youth. In addition to Dr. Wright and Dr. Chen, Assistant Professor Ching-Hsuan Lin and PhD candidate Chin-Wan Wang from NTU were invited to join the collaborative project. Dr. Margaret Spencer and Dr. Sonja Van Wichelen from USYD are also a part of the research team. The main goals of this collaboration encompass research and teaching and include establishing an enduring institutional tie between the Department of Social Work at NTU and the School of Education and Social Work at USYD.

This collaboration seeks to increase knowledge and awareness of intercountry adoptions and hopes to develop implications for practice and policies. There are two aspects—one central to Australia and one to Taiwan—to the research focus in this project. Cross-cultural and identity issues have been a primary point of discussion in intercountry adoptions. In terms of the Australian aspect, previous studies have found that interracial adoptees often experience
confusion about their ethnic/racial identity as well as challenges handling discrimination. Thus, adoptive families need guidance and support regarding how to support their child’s adoption- and ethnicity-related identity issues over the course of childhood, adolescence, and young adulthood. Connections with families and countries of their origin and discovering their own personal identity are part of the lifelong journey for internationally adopted persons. In terms of the Taiwanese aspect, birth families involved in intercountry adoptions have received little attention in the literature; therefore, it is critical to better understand their awareness and perspectives on adoption to provide professional support in the adoption process.

The most spectacular part of this collaborative research is giving voice to the birth mothers involved in intercountry adoptions, who have been described as the “forgotten member of the intercountry adoption triad.” There are deep social justice concerns regarding intercountry adoptions. These adoptions typically involve, on one side, desperately poor mothers who may be members of less privileged racial and ethnic groups, and on the other side, wealthy white adoptive parents in developed countries (Bartholet, 2005). Birth mothers involved in intercountry adoptions may not fully understand the implications of signing documents that sever the legal relationship with their child, allowing for their child’s emigration and adoption (Manley, 2006). This research also attempts to explore the concept of openness, which is a standard feature of domestic adoptions within Australia but is lacking in intercountry adoptions. Open adoptions allow the child to receive information and retain links to their birth family, and has evolved as a practice through recognition that people have an inherent drive to know their origins to develop a coherent narrative identity (Grotevant, & Von Korff, 2011). In contrast, traditional intercountry adoptions are closed, with no ongoing contact between the birth families, adopted persons, and adoptive families.

Data will be collected in both countries. Interviews will be conducted in Australia with adoptees from Taiwan and their adoptive parents to learn about their experiences, the services and support they have received, and efforts they have made to promote the adoptees’ cultural socialization. In Taiwan, interviews with original family members will be conducted to learn about their opinions regarding services in the adoption process, issues related to reunion, and services they needed after adoption. In addition, focus groups will be conducted with adoption case-workers involved in the process.
of intercountry adoption to gain an understanding of the current services and challenges. This effort is expected to fill the gaps in knowledge in intercountry adoptions between Taiwan and Australia and allow more voices to be heard via qualitative data presentation. We also hope to contribute to the literature on intercountry adoption, particularly with regard to cross-cultural adjustment, post-adoption services, and reunion issues.

An iterative research process will be used to guide the collaboration so that emerging findings from research in both countries will inform subsequent stages of the project. Through quarterly teleconference meetings, interviews with stakeholders, symposiums or seminars to present findings, and other collaborative tasks, the research team will share findings, receive feedback and work together more efficiently. This project will also culminate in two symposia, one hosted in Taiwan and the other in Australia, to disseminate the findings to academics, social work professionals, and policy makers. The entire research team will present at both events and will share their perspectives on intercountry adoption. Research participants, such as adopted persons, birth family members, adoptive parents, and/or adoption professionals, will be invited to speak at both events, representing the views of important stakeholders. In advance of each symposium, a media release will be issued to inform policy makers and the field about how people are involved with adoption (the child, adoptive family, and birth family).

Findings from this research will also inform joint curriculum development. A curriculum module on adoption will be co-developed and integrated into the social work degrees at both institutions. This module will also be disseminated through the national associations of social work in both countries to enhance professional understanding of adoption and working with birth families, adoptive families and adopted children. This curriculum module will capture the voices of birth and adoptive families and children, drawing on direct quotations from the interviews. Learning outcomes will include building awareness and knowledge of how to support adoption, including the longer-term cultural identity of adopted children.

These research and teaching collaborations will build strong institutional ties between the social work programs at NTU and USYD. The project will establish a joint track record of publications among the NTU and USYD researchers that will support the development of competitive grants from foundations or other sources. This exploratory research will identify future areas of research related to the well-being of adopted children and their birth and adoptive families. It is also expected to inform professional practice in both Taiwan and Australia, including implications for connecting the diaspora of Taiwanese-born Australian adoptees and their adoptive families in Taiwan so that they can support their children’s cultural identities. The research team will seek media coverage in both Taiwan and Australia, which will highlight the partnership between NTU and USYD as well as enhance public awareness of the needs of adopted children and their birth and adoptive families.

Additionally, the team-based collaboration, exploring and linking both sending and receiving countries, is likely to gain international recognition and may pioneer a collaborative model for other countries involved in intercountry adoptions, such as the United States. Findings from the research will include multiple angles on intercountry adoption and represent the perspectives of adoptees, adoptive families and birth families, as well as the professionals who facilitate and support adoptions. These findings are likely to be of interest to policy makers and adoption practitioners. There has been little to no research on the perspectives of birth mothers in intercountry adoption; thus, this aspect of the research will be groundbreaking.

The two-way collaborative relationship between NTU and USYD is off to a good start, and will continue to address more issues related to intercountry adoption after the launch of the joint project. We anticipate an abundance of research, practice, teaching and policy reforms in the future.

References


Historical narratives in the pre-Qin and Han periods

The long history of Chinese historical narratives that originated in the Shang-Zhou (商周) era, bloomed in the Warring States (戰國) period and prospered in the Han (漢) dynasty generated the greatest amount of narrative literature in the world. This book explores and discusses the pre-Qin (先秦) and Han historical narratives through Confucian classics and their commentaries, Chinese philosophy, Chinese historiography, and unearthed documents.

The research methodology focuses on Zuo Zhuan and Guoyu with the assistance of The Tsinghua Bamboo Slips: Xinian and The Shanghai Museum Bamboo Slips: Gucheng Jiafu, as well as the Confucian scholars’ previous studies. The author adopts the concepts of “Narratology” and “Hermeneutics” using a combination of traditional Confucian classics, history and the article study. By using both macroscopic and microscopic methods, this book investigates the origin and features of, as well as the inherited changes (including historical and cultural implications) in, Chinese historical narratives.

This book examines the characters, such as Duke Yin of Lu (魯隱公), Duke Wen of Jin (晉文公), Duke Jing of Jin (晉景公), Duke Li of Jin (晉厲公), Duke Ping of Jin (晉平公), King Zhao of Chu (楚昭王), Confucius (孔子), Zichan (子產), Shusun Muzi (叔孫穆子), Zhao Dun (趙盾), Cui Zhu (崔杼), Luan Shu (欒書), Xun Yan (荀偃), Han Jue (韓厥), Xi Zhi (郤至), Luan Ying (欒盈), Fan Gai (范鞅), and Fan Yang (范鞅). In addition, this book reviews plots and subjects such as “Zhongni Yue (Confucius’s speech) narratives,” “war narratives,” “regicide narratives,” “metaphorical narratives,” “god-and-demon narratives,” “the demise of the Xi clan,” and “the fall of the Luan clan”.

This treatise is more comprehensive and diverse than most of the literature on the pre-Qin and Han historical narratives.

Reference
Long-Shien Lee (2017). Historical Narratives in the Pre-Qin and Han Periods. 先秦兩漢歷史敘事隅論. Taipei: National Taiwan University Press.

Professor Long-Shien Lee
Department of Chinese Literature
leels@ntu.edu.tw
Why should a guidebook, not a textbook, be written on Xunzi studies?

This volume is neither an introduction to Xunzi’s (ca. 315-235 BCE) philosophy nor a collection of those research articles and essays that the author has conducted on the topic. It is instead a guidebook to “Xunzi Studies” and the research on Xunzi’s philosophy. I wrote this book mainly for those who conduct scholarly research about Xunzi or for those who must address his philosophy to discuss more popular thinkers such as Mencius (ca. 390-310 BCE) and Zhuangzi (?-?, late contemporary to Mencius) or other Chinese philosophy-related topics in their studies.

Given the stated purpose for publishing this work, particularly in light of the current adverse circumstances for commercially publishing humanities research monographs in Taiwan, one may wonder how many readers, in addition to university libraries, would be willing to purchase such a book, as the scope of content of this volume is so narrowly planned (i.e., guidebook for Xunzi research). Among students of Chinese philosophy during the past century, Xunzi has definitely not been popular. Indeed, his philosophy has been continuously criticized. In East Asian intellectual traditions, in which Neo-Confucianism has dominated as a state and sociopolitical ideology, owing to his “human nature is bad” theory, Xunzi’s philosophy has even been regarded as a harmful heterodox, especially compared to Mencius who advocated that “human nature is good.” In Taiwan, Xunzi has only recently been discussed in a more-or-less fair and composed manner, while during the same period in mainland China, “Xunzi” has rapidly grown into a very popular topic in Chinese philosophy and history.

From this perspective, the reasons that I have attempted to present a guidebook for Xunzi studies are threefold. First, in this book, I intend to reaffirm the claim that Xunzi has been a very important thinker during the entire two millennia of East Asian history and will outline his philosophical insights as they relate to many of this century’s humanity issues. The huge impact of Xunzi’s philosophy on intellectuals and the history of the whole East Asian region has been compared with that of Aristotle by several eminent early Chinese philosophy scholars such as Homer H. Dubs (1892-1969) and Chen Daqi (1886-1983). For instance, the significance of Xunzi’s idea of Liyi (rule for proper conduct) can be best illuminated by comparing it with Aristotle’s idea of dikaios (justice). Xunzi’s intellectual role in the history of China and East Asian countries should be evaluated more fairly, much as Aristotle’s role is evaluated in the West.
Second, despite the aforementioned importance of his philosophy, among Xunzi specialists, Xunzi is widely considered to be the most misunderstood philosopher and the most depre- cated Confucian thinker among the Warring States’ masters during the classical period. More importantly, the prejudice against Xunzi by supporters of Mencius’ position has created a serious misunderstanding in mainstream Chinese philosophy, such that Xunzi’s disbelief in the potential- ity of human nature has opened the door for the rise of Legalism, thereby leading to the advent of a dynastic totalitarian rule. It would be unfortunate if 21st century Xunzi studies continued to perpetuate such a misunder- standing.

Third, although it sounds paradoxical because I have just mentioned Xunzi’s unpopularity among other Chinese thinkers, the continued popularity of “Fe- ver for Learning the Classics” (Guoxue re) since the 1990s in mainland China has definitely promoted a new style—e.g., a less ideological, more philological analysis—of studies of Xunzi’s philosophy. The rapid growth of scholars and students has been followed by a remarkable expansion in the number of scholarly articles and monographs on Xun- zi. Such a transformation of the research environment has made it difficult for newcomers to this research area to find the most relevant and helpful materials for their own research topics. To date, there are more than 5000 items that are related to Xunzi, such as commentaries, modern translations, monographs and scholarly articles. Ironically, a search for the term “Xunzi” in a major database can return hun- dreds of Xunzi-related materials and articles. How can those graduate students and “begin- ners” to this subject distinguish the references that are essential from those that are not? For the past several years, the flood of secondary materials on Xunzi has become an obstacle for further developing Xunzi research. In this sense, graduate students, and especially young researchers beginning to study Xunzi-re- lated topics in their academic research, desperately require a big picture understanding of the state of affairs of Xunzi studies. Such a purpose cannot be attained by treating this volume as a textbook that summarizes Xun- zi’s philosophy but can if this is a guidebook that helps readers reflect on how to address the present conundrum in Xunzi studies.

In summary, throughout this volume, I help readers find more efficient ways to conduct their own research on Xunzi-related subjects rather than directly imposing my own interpretations upon them of his life, texts, or the characteristics of his philosophy. Few Taiwanese scholars today spend much effort publishing this type of monograph because a large part of this volume mainly consists of so-called “review articles,” which are usually ranked as “miscellaneous” under the current formal standard in the ROC’s scholarly evaluation sys- tem; thus, the whole volume can appear to be no more than a mosaic of review articles. However, investing a great effort to realize what I deeply believe in from my own academic standards, regardless of how much score the evaluation system gives to it, is the most important goal of my academic life. Additionally, to publish such a book would meet what I would call the “NTU spirit”!

Reference

Professor Masayuki Sato
Department of Philosophy
msato@ntu.edu.tw
Climate change and societal risk
An introduction to Sociology of Climate Change

In modern society, nation states have faced various challenges, including housing bubbles, pollution, and unemployment, due to economic, environmental, and social risks. Generally, the modern state promotes technology to resolve social problems (e.g., promoting genetically modified organisms (GMOs) to secure food supplies) and thus justifies its legitimacy (Chou, 2014). The state seeks to secure basic human rights via technology and economic progress, hoping this will convince the people to pledge their loyalty to the nation state and maintain their faith in representative democracy.

However, the contradiction between economic growth and environmental protection in the context of globalization has led to unintended consequences. Since the 1980s, the chemical and petrochemical industries have been the main industries triggering exports and economic growth among developing states (Chou, 2015) despite these industries’ high pollution levels, high energy consumption, high water consumption, and high carbon emissions. The consequences include the mass destruction of the ecological environment, the development of dangerous scientific industries, and pollution due to high scientific uncertainties, which all contribute to global climate change (Chou, 2017).

Facing the challenges of globalization and climate change, Ulrich Beck argues that risks and side effects caused by the industrial society are not only local or regional but also cross-national and result in irreversible global consequences. At the spatial level, the consequences of nuclear risks are not limited to any single location, making the risk omnipresent. At the temporal level, the risk is in not knowing what will happen: the ‘unknown unknowns’ (Beck, 2006). At the social level, because the new risks are intertwined with many factors involved in global economics, their causes cannot be precisely determined, and their effects are not reversible. Therefore, the risk is incalculable.

In the context of global climate change, Beck thus argues that 'methodological nationalism', as the core of traditional sociology, cannot address global risks comprehensively. Methodological nationalism assumes that the nation, state and society are the natural social and political forms of modern society. However, the cross-boundary risks and manufactured uncertainties have already penetrated the boundaries of nation states and academic disciplines. For example, the health impacts, environmental impacts, and social impacts of extreme weather cannot be governed by any single agent, organization, group, or any single discipline. Essentially, in the age of global climate change, the new paradigm is no longer limited to a unilateral scientific principle but must expand professional knowledge. The new paradigm not only integrates various scientific principles but also seeks new social science methodologies for better risk governance (Chou, 2015).

In this regard, the Sociology of Climate Change aims to respond to Beck’s proposal to address global plights from the cross-disciplinary perspective of methodological cosmopolitanism. The author, Professor Chou Kuei-Tien, identifies the role of regulatory science in the context of Taiwan. Chou argues that in Taiwan, a culture of technocracy took root in the Cold War era as a solution to rapid modernization. Hence, Taiwan has become...
a kind of double risk society — a regime of expert politics with hidden and delayed risk. On the one hand, scientific elites manage risks with the ideology of positivism. On the other hand, social, environmental, and economic risks have been ignored or deemphasized for decades.

Chou further analyzes Taiwan’s current risk society from the following perspectives. First, Chou analyzes the local carbon, water, and energy-intensive industries, particularly the petrochemical and steel industries. Chou then identifies that, historically, due to the path dependency, Taiwan’s society failed to follow a successful industrial transition to reduce reliance on the high-carbon industrial structure.

Second, Chou addresses the issues of Taiwan’s public perceptions and actions toward climate change and air pollution. According to the studies, most of the public are aware of the seriousness of climate change and air pollution. Finally, Chou probes the actions of civil society and the environmental movement. Chou argues that in recent decades civil knowledge and risk discourses have grown as a response to climate change. As a result, the environmental movement in Taiwan has gradually become a significant social power, challenging the technocratic regime over the past decade. Through antipollution appeals, local communities have grown from simple NIMBY (Not In My Back Yard) protesters into systematic civic groups equipped with solid scientific knowledge and able to resort to strategic actions. The Taiwanese government’s failure to handle environmental risk has engendered tensions between the state and civil society and compromised the state’s legitimacy, as is shown by the emergence of a civic environmentalism that has challenged the persistent technocratic government in recent years. [1]

The new Taiwanese government designed the ‘2025 nuclear free homeland’ roadmap in 2016 to address problems in carbon reduction with energy transition, industrial transition, and the reduction of air pollution. However, so far, this proposal does not aim to construct a new energy paradigm but rather maintains the conventional ‘hard path’ of energy development. For example, the new government has not clarified solid strategies for promoting ‘prosumer’ energy systems and roadmaps for the petrochemical and steel industries.

Therefore, a model capable of accelerating the formation of a new energy paradigm is required. Chou suggests a project entitled the Sociology of Climate Change with the following themes:
1. Climate change and cosmopolitanization with institutional and political metamorphosis.
2. Climate change and a high-carbon society.
3. Climate change and the transformation of a regime of expert politics with hidden and delayed risk.
4. Climate governance and public awareness.
5. Climate governance and social movements.

Footnote
1. According to Oxford dictionaries, the definition of Nimby is “A person who objects to the siting of something perceived as unpleasant or hazardous in their own neighbourhood, especially while raising no such objections to similar developments elsewhere”. See https://en.oxforddictionaries.com/

References

Professor Kuei-Tien Chou
Director, Risk Society and Policy Research Center, College of Social Science
Professor and Director in the Graduate Institute of National Development
ktchou@ntu.edu.tw

Dr. Yeng-Chieh Tsai
Postdoctoral Researcher, Risk Society and Policy Research Center, College of Social Science
jaytsai@rsprc.ntu.edu.tw
‘Micro’ organism, ‘macro’ problems

Studies of the MERS-CoV macro domain conducted by NTU structural biologists reveal a promising new therapeutic target.

The macro domain is a well-known protein module with an affinity for ADP-ribose. RNA viruses such as severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV encode macro domains in their genomes, and the structures of several viral macro domains have been reported. However, the critical piece of the puzzle for the molecular structure and functional relationship of the viral macro domain remains missing.

SARS infamously emerged and resulted in 774 deaths in 2003. Ten years later, another potentially deadlier disease called MERS, also known as camel flu, has caused over 400 deaths since the first confirmed case was reported in Saudi Arabia in 2012. MERS is caused by a coronavirus that closely resembles the SARS virus but exhibits a much higher mortality rate; 40% of patients infected with MERS die, compared to 10% of patients infected with SARS. An effective treatment that cures MERS, an emerging disease that was recently discovered in 2012, is not available. Supportive care, including organ support to prevent complications, organ failure and secondary infections, remains the main treatment for MERS. Although many inhibitors targeting viral components that play critical roles in MERS-CoV replication have been reported, most of them are still in the early phases of investigation. The application of neutralizing monoclonal antibodies against MERS-CoV requires a high investment and rigorous testing and must undergo an approval process. Combinations of antivirals, interferons and corticosteroids have been used to treat patients infected with MERS, but none of them have resulted in a significant effect on clinical outcomes. Notably, the major challenge facing clinicians is the lack of specific anti-viral drugs with proven efficacy toward MERS.

Professor Chun-Hua Hsu’s research team from the Department of Agricultural Chemistry and the Genome and Systems Biology Degree Program has recently focused on understanding the structural features of these functionally diverse macro domains from various microorganisms. A conserved macro domain near the N-terminal region of non-structural protein 3 with unknown function was identified using bioinformatics analysis. According to Mr. Chao-Cheng Cho, a Ph.D. candidate from the Hsu lab, “Since MERS-CoV is a newly identified virus, we are curious about the existence of structural and functional divergences between macro domains from MERS-CoV and other CoVs”.

The macro domain is a protein module comprising approximately 180 amino acids that bind to the ester ADP-ribose to regulate cellular processes such as DNA repair, gene expression and controlled cell death. Recently, the macro domain from SARS-CoV, a coronavirus related to MERS-CoV, has been reported to suppress host immunity through...
its de-mono ADP-ribosylation activity. Using structural and biochemical approaches, Hsu’s team discovered that MERS-CoV has a higher binding affinity for ADP-ribose than the macro domains from the CoVs that have been characterized to date. An interesting question has been raised: Does the higher binding affinity of the MERS-CoV macro domain for ADP-ribose account for the four-fold higher mortality rate observed in patients infected with MERS-CoV than in patients infected with SARS? This question will be answered in further investigations of the roles of the macro domain in MERS-CoV infection.

Professor Hsu’s lab will conduct structure-based screens for potent inhibitors of the MERS-CoV macro domain using known drug databases and the traditional Chinese medicine database and will attempt to elucidate the inhibitory mechanism using biophysical techniques.

Quadruplex formation enhanced by DNA methylation

Expression of the human telomerase reverse transcriptase gene is modulated by quadruplex formation in its first exon due to DNA methylation

It is well known that DNA secondary structure and methylation are involved in regulating gene expression in mammals. Research has shown that G-quadruplex (G4) structures, which are among the most prevalent non-B DNA structures, are key players in the control of gene transcription and regulation. Methylation of cytosine in CpG dinucleotides in promoter regions is a well-characterized epigenetic modification that plays an important role in regulating numerous cellular processes, including development and tumorigenesis. CpG dinucleotides are often found within potentially G4-forming sequences in the promoter regions of numerous genes. Although early research indicated that CpGs within higher-order G4-forming DNA motifs undergo low methylation, methylation of cytosines in CpG dinucleotides within these G4 motifs nonetheless occurs in the genome. However, the interplay between DNA methylation and DNA secondary structures and the resulting effects on the regulation of gene expression have not been addressed.

Our study began from the finding that oxidative stress mediated by photodynamic therapy (PDT) and chemotherapy can down-regulate the expression of human telomerase reverse transcriptase (hTERT). hTERT is the major component of the catalytic subunit of telomerase and acts as a rate-limiting factor for telomerase activity. Telomerase activity is observed in approximately 90% of human cancers, whereas most somatic normal tissues are negative for hTERT expression. Aberrant hTERT gene expression may cause aging, cancer, and other diseases. Several transcription factors with binding sites in the promoter region have been documented to directly or indirectly regulate
hTERT gene expression, including the activators MYC and SP1 and repressors such as p53 and CCCTC-binding factor (CTCF). Many recurrent mutations within the promoter region of hTERT have been identified in various cancers; such mutations correlate with elevated hTERT transcriptional activity. However, no mutation or single-nucleotide polymorphism has been identified within the CTCF binding site in the first exon of hTERT. Interestingly, methylation of the first exon of hTERT prevents CTCF binding and allows for hTERT gene expression in telomerase-positive cells. However, the underlying mechanism by which methylation regulates hTERT gene expression remains unclear.

Two findings led to our interdisciplinary research to address the interplay between DNA methylation and secondary structure. First, oxidative stress mediated by PDT and Taxol treatment altered the DNA methylation profile within the CTCF-binding region in the first exon of hTERT. Second, four CpG dinucleotides with the potential to form a G4 structure were identified in the G-rich sequence $G_3A$GC$CAGCGCTCGCAGCGC_4$, which is located at +13 to +37 within the hTERT CTCF-binding region (Figure 1a; this sequence has been named hT25). This sequence was identified by a group led by our collaborator Dr. Ta-Chau Chang at Academia Sinica. Without the cooperation of multidisciplinary teams, we would be unlikely to discover a possible novel mechanism for regulating gene expression.

We first conducted a 1D imino proton NMR experiment to address the possible formation of hydrogen bonds of DNA secondary structures and thereby assess the potential for G4 formation in hT25. Imino proton NMR results for hT25 showed the competitive existence of two types of secondary structures: hairpin and quadruplex structures (Figure 1b). A particularly interesting finding was that the imino proton signals indicative of the G4 structure were more pronounced after CpG methylation (Figure 1c). Further experiments demonstrated that methylation of the fourth of the four CpG dinucleotides in hT25 ($C_3G_2$) plays a key role in enhancing quadruplex formation. Furthermore, in tests with reporter constructs, we confirmed that expression was markedly higher for methylated reporter constructs than for wild-type constructs, a finding consistent with our chromatin immunoprecipitation (ChIP) results showing a significant reduction in CTCF binding after methylation. These results clearly indicate that methylation of CpG dinucleotides indeed inhibits CTCF binding and results in gene expression. However, it is unclear whether the quadruplex structure promoted by methylation has a major effect on CTCF binding and gene regulation.

![Figure 1. Characterization of DNA secondary structures of a G-rich sequence in the first exon of the hTERT gene.](image-url)

- a) Identification of the potentially G4-forming sequence hT25, d(G3GCACGCTCGCAGCGC), in the antisense strand (from +37 to +13) in the first exon of the hTERT gene, which is located within the CTCF-binding region.
- b) and c) Imino proton NMR spectra of hT25 (b) and hT25-Me (c) in Tris-HCl buffer without (bottom panel) and with (top panel) 150 mM KCl. In the methylated sequence hT25-Me, cytosine was synthetically modified to 5-methylcytosine at the four CpG dinucleotides of hT25.
We further designed four hT25 mutants to examine the formation of this sequence into a G4 structure and to assess its effect on CTCF binding in the regulation of hTERT gene expression. hT25-m1 and hT25-m3 were designed to disrupt quadruplex formation, and imino proton NMR results for these mutants revealed no appreciable signals of quadruplex structure, implying that hT25-m1 and hT25-m3 preferentially form hairpin structures. In contrast, hT25-m2 and hT25-m4 have imino proton NMR spectra with distinct signals of quadruplex structures. Electrophoretic mobility shift assay (EMSA) studies confirmed that CTCF binding was perturbed for hT25-m2 and hT25 structures with methylated CpG dinucleotides; in contrast, significant CTCF binding was observed for hT25-m1 and hT25-m3. The reporter expression level was much higher in A375 cells transfected with a plasmid containing hT25-m1 or hT25-m3, both of which preferentially form a hairpin structure. Furthermore, ChIP analysis revealed that the level of CTCF binding is markedly lower in cells transfected with the hT25-m2 or hT25-m4 plasmid than in WT cells or cells transfected with the hT25-m1 plasmid. These results indicated that hairpin and quadruplex structures play an important role in CTCF binding to hTERT and hTERT gene expression. Notably, DNA methylation alone is not sufficient to inhibit CTCF binding to the first exon of hTERT, suggesting that quadruplex formation promoted by CpG methylation plays a major role in preventing CTCF binding and further regulating gene expression.

In summary, the key finding of this study is that methylation of cytosine at specific CpG dinucleotides participates in quartet formation, which can shift the equilibrium from a hairpin structure to a quadruplex structure via a simple flipping process (Figure 2). CTCF prefers to bind to the hairpin structure, and this binding suppresses hTERT transcription; in contrast, quadruplex formation inhibits CTCF binding, resulting in hTERT gene expression. Our results not only identify a new example of quadruplex formation induced by CpG dinucleotide methylation but also provide mechanistic insight into the regulation of gene expression.

Reference
Pei-Tzu Li, Zi-Fu Wang, I.-Te Chu, Yen-Min Kuan, Ming-Hao Li, Mu-Ching Huang, Pei-Chi Chiang, Ta-Chau Chang, and Chin-Tin Chen (2017). Expression of the human telomerase reverse transcriptase gene is modulated by quadruplex formation in its first exon due to DNA methylation. Journal of Biological Chemistry, 292(51), 20859-20870. DOI:10.1074/jbc.M117.808022.

Professor Chin-Tin Chen
Department of Biochemical Science and Technology
chintin@ntu.edu.tw

Figure 2. Proposed mechanism of CTCF binding to the first exon of the hTERT gene for transcriptional regulation. CTCF favors binding to the hairpin structure, whereas quadruplex formation, which is enhanced by CpG methylation, impedes CTCF binding and leads to gene expression.
An integrative tool for phosphoproteomics
A key in systems biology

Systems biology is a data-driven science in which a combination of experimental and computational approaches are used to understand complex dynamic biological systems from a systems-wide perspective. Systems biology integrates various omics data, including genome, transcriptome, proteome and metabolome information, and explores the complex interactions among many levels of biological information to understand how these levels work together. Knowledge regarding interacting protein and signaling networks provides researchers with a basic understanding of the molecular mechanisms of cell and tissue function and can also contribute to the development of new drug targets, drugs and combination therapeutic strategies.

Protein functions determine cellular functions; therefore, the proteome, which was first introduced in 1996 by Mark Wilkins as an analog to the genome and is defined as the entire complement of proteins expressed in a cell, tissue or organism in a specific state, provides the most important type of omics data. Post-translational modifications (PTMs) are protein modifications that occur in almost all proteins and play important roles in various biological processes. Over 200 protein PTMs have been described. Protein phosphorylation is one of the most important PTMs in cells. Protein phosphorylation modifies protein substrates at specific amino acid residues to regulate cell signaling transduction and modulate protein-protein interactions. Analysis of the dynamic phosphoproteome is crucial for understanding cell signaling but remains challenging. Professor Hsueh-Fen Juan’s team developed an integrative user-friendly web tool, DynaPho (http://dynapho.jhlab.tw/), for the analysis of time-series phosphoproteomics data.

DynaPho contains six analytical modules: data summary, profile clustering, function enrichment, dynamic network, kinase activity and correlation analysis. In the “data summary” module, DynaPho provides the distribution of phosphorylated residues and phosphorylation ratios as well as the phosphorylation trend for a set of phosphosites. Users can obtain clustered profiles in the “profile clustering” module. The “function enrichment” module performs a Gene Ontology (GO) enrichment analysis of phosphoproteomic data for each time point. The “dynamic network” module provides time-dependent interaction networks based on users’ phosphoproteomics data and protein-protein interactions. The “kinase activity” module of DynaPho helps users infer kinase activity at each time point. The “correlation analysis” module of DynaPho facilitates the identification of known and novel kinase/phosphatase-substrate relationships and the visualization of kinase/phosphatase-phosphosite association networks.

Figure 1. The six modules in the DynaPho web tool: data summary, profile clustering, function enrichment, dynamic network, kinase activity and correlation analysis.
DynaPho can be applied in studies of various organisms and has successfully facilitated the exploration of drug response networks in cancer cells, hormone-regulated phosphosignaling in plants and molecular functions in cells. The drug response network research revealed that the drug citreoviridin induced mitogen-activated protein kinase/extracellular signal-regulated kinase signaling in lung cancer cells to suppress cancer cell growth and provided perspectives regarding cancer therapeutic strategies. The aforementioned research on hormone-regulated phosphosignaling in plants dissected the dynamic regulation of brassinosteroids in Arabidopsis and expanded our knowledge of protein phosphorylation regulation. In studies of molecular functions in cells, DynaPho can be used to identify key phosphoproteins and their regulated networks. This tool contributes to the enhanced use of time-series phosphoproteomics data by providing easy-to-understand visuals and information regarding condition-specific cellular signaling.

References

Professor Hsueh-Fen Juan
Department of Life Science yukijuan@ntu.edu.tw

Assembly of recombination-mediated DNA repair machinery

How cells maintain their genome integrity is our long-term interest. The genome is constantly exposed to various endogenous and exogenous insults, ranging from endogenous replication stress to exogenous ultraviolet light and carcinogens. These insults cause a variety of DNA damage. DNA double-strand breaks (DSBs) are the most lethal chromosomal lesion if not repaired properly. DSBs trigger genomic instability and halt DNA replication. Cells have developed evolutionarily conservative mechanisms to repair DSBs and maintain genome stability. Dysregulation of DSB repair pathways causes cell death or diseases such as cancers.

Non-homologous end joining (NHEJ) and homologous recombination (HR) are the two major DSB repair pathways. NHEJ is an error-prone repair pathway that simply promotes religation of two broken ends. In marked contrast, the homologous recombination-mediated repair pathway is a precise repair mechanism. Notably, recombination machinery is also a prerequisite for stabilizing and reinitiating stalled/collapsed replication forks during replication stress. Thus, dysfunction in HR leads to chromosome fragility and cancer susceptibility.

Mechanistically, HR induced by DSBs is catalyzed by RAD51 recombinase. RAD51 polymerizes ssDNA generated from DSB sites to form a helical filament known as the presynaptic filament and then catalyzes the homology search and DNA strand exchange reaction (Figure 1). During HR, RAD51 activity is tightly regulated by several associated partners, including BRCA1/2, PALB2, RAD51 paralogs, RAD51AP1, and the SWI5-SFR1 complex. These interactions raise intriguing questions regarding how these accessory factors influence RAD51 activity mechanistically and how they coordinate with each other. My laboratory is dedicated to addressing this issue using biochemistry, biophysics and cell-based approaches.

Our research work has made a significant contribution to the understanding of the mechanism...
by which the mammalian SWI5-SFR1 protein complex stimulates RAD51-mediated DNA repair. Genetic analyses have provided evidence that SWI5 and SFR1 function as a complex to facilitate RAD51-dependent recombination repair. This repair mechanism is evolutionally conserved from yeast to mice to humans. Consistent with genetic findings, our biochemical and biophysical analyses have demonstrated that the heterodimeric SWI5-SFR1 complex physically interacts with RAD51 and enhances the RAD51-mediated strand exchange reaction (1). Importantly, we have provided evidence that the enhancement of RAD51 activity stems from a dual function of the SWI5-SFR1 complex, namely, stabilizing the presynaptic filament and enhancing the release of ADP from the filament to maintain the presynaptic filament in its active, ATP-bound form (2). Most importantly, we provided evidence that SWI5-SFR1 interacts with the oligomeric, but not monomeric, form of RAD51. We further identified a mutant variant of SWI5 that forms a complex with SFR1 but abolishes the interaction with RAD51. Our biochemical analyses documented that this mutant variant lacks the abilities to stabilize the presynaptic filament, facilitate ATPase activity by RAD51, and stimulate RAD51-mediated DNA strand exchange. Our results demonstrated that the stimulatory effect of SWI5-SFR1 on RAD51 activity stems from the physical protein-protein interaction (3; Figure 2).

Most importantly, knowledge of recombination-mediated DNA repair obtained from bench work has been translated into clinical use for the prevention and treatment of various cancers that arise due to recombination repair deficiency. Hereditary genetic mutations in recombination repair genes, such as BRCA1, are associated with a significantly high incidence of breast and ovarian cancers. Angelina Jolie, the famous American actress who harbors a hereditary BRCA1 mutation, chose prophylactic surgery for cancer prevention. In addition to cancer prevention, cancer cells with recombination repair deficiency are sensitive to PARP inhibitors, such as olaparib (Figure 3). Thus, diagnosis of recombination repair capacity in cancers will assist in the selection of a specific drug to achieve personalized medicine. In summary, our research on repair mechanisms has great application value for precision medicine.

Figure 1. RAD51-mediated homologous recombination repair
The DNA double-strand break (DSB) is resected to generate 3’ ssDNA overhangs. Invasion of a homologous DNA molecule by a RAD51 filament yields a DNA exchange reaction. Following DNA synthesis and DNA ligation, the DSBs are repaired.

Figure 2. Model depicting the mechanisms of SWI5-SFR1 in RAD51-mediated DNA repair
Our study represents a significant conceptual advancement in understanding the mechanistic underpinnings of RAD51-SWI5-SFR1-dependent chromosome damage repair.
Developmental changes in conceptual processing in children with autism

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by deficits in social communication. To explore the developmental changes in communication deficits in ASD, a sample of children encompassing a wide age range, from childhood to adolescence, was recruited. Regarding neural substrates of language/communication in ASD, recent studies have shown aberrant neural activity during semantic processing. For example, there is reduced activation in the left inferior frontal gyrus in adults with ASD compared with that in healthy controls. In contrast, individuals with ASD often have a perception-based preference with recruitment of primary sensory cortices.

A meta-analysis (Lai et al. 2014) concluded that, in contrast to typically developing (TD) individuals, who focused on top-down control processing with recruitment of the frontal cortices for language/communication, individuals with ASD usually engaged more in bottom-up pro-

References

Associate Professor Hung-Yuan (Peter) Chi
Institute of Biochemical Sciences
peterhchi@ntu.edu.tw
cessing because they possessed enhanced sensory-perceptual processing of local features of the stimuli. At the neural level, individuals with ASD showed enhanced activity of the primary sensory cortices (i.e., primary visual cortex) and reduced activation in the frontal area, which is involved in top-down processing (Lai et al., 2014). These findings imply that, unlike healthy adults, adults with ASD might recruit an immature, perception-based neural mechanism to support semantic processing instead of engaging in a frontal control mechanism.

We aimed to examine age-dependent neural correlates of semantic processing in boys with ASD and TD boys. We used functional magnetic resonance imaging (fMRI) to investigate 37 boys with ASD (mean age = 13.3 years, standard deviation = 2.4) and 35 age-, sex-, intelligence quotient- and handedness-matched TD boys (mean age = 13.3 years, standard deviation = 2.7) from age 8 to 18 years. Previous research has shown that adolescents aged 13-17 might have a better ability to perform semantic tasks than children aged 8-12. Thus, we further divided the participants into adolescent (22 ASD and 21 TD, mean age = 15.07 years, age range = 13-18) and child (15 ASD and 14 TD, mean age = 10.67 years, age range = 8-12) groups.

The participants performed a semantic judgment task while they underwent an MRI scan. They were asked to indicate whether pairs of visually presented Chinese characters were related in meaning. Group (ASD, TD) x age (adolescent, child) ANOVA was performed to examine differences in age-related changes. Direct comparisons between the adolescent group and the child group were also performed. The behavioral results showed that the ASD group had lower accuracy in the related condition than the TD group. The neuroimaging results showed greater activation in the cuneus and less activation in the left inferior frontal gyrus in boys with ASD than in TD boys. Further examination of the developmental changes revealed that children with ASD had greater activation in the cuneus than TD children, whereas adolescents with ASD showed reduced left inferior frontal activation compared with that in TD adolescents.

In conclusion, TD boys may engage more in higher-level processing during the retrieval or selection of semantic features, whereas boys with ASD may rely more on lower-level visual processing during semantic judgments. These findings imply different functional organization of the semantic system between the two groups.

References

Professor Tai-Li Chou
Department of Psychology, Imaging Center for Integrated Body, Mind and Culture Research tlcou25@ntu.edu.tw

Figure 1. (a) The interaction effect (group by age) for activation. (b) Children with ASD had greater cuneus activation than TD children (blue), whereas adolescents with ASD showed reduced left inferior frontal gyrus (IFG) activation compared with that in TD adolescents (green).
Humans exhibit a remarkable cognitive flexibility to adapt to novel contexts. This great flexibility for new contexts relies on three cognitive abilities in concert. First, one must maintain goal-relevant representations in working memory (WM). Second, achieving one’s goal depends on the anticipation of upcoming events, and one must act in such a way that the future outcome will be in accordance with the desired outcome. Third, such anticipation relies on one’s past experiences associated with goal-relevant information for a particular context. Together, one must use past experiences or prior knowledge to prepare for appropriate actions while adjusting behaviors toward the goal based on the context.

WM allows us to hold and manipulate information that is relevant to our current task goals for a given contextual episode over a short period of time. The critical role of WM is to bridge the gap between perception and higher-level mental processes such as long-term memory, thinking, reasoning, and language. However, the capacity of WM is highly limited. While previous investigations have revealed that attention is important in controlling the contents of WM, it remains unexplored whether task context can influence WM. This study aimed to investigate whether context-driven selection history can modulate the efficacy of attention allocation in WM (Kuo, 2016). In this study, the participants performed a visual WM task in which a display of one item (low WM load) or three/four items (high WM load) was shown for the participants to hold in their WM. Following a short retention interval, the participants judged whether a probe item was in the memory display. Selection history was defined as the number of items attended across trials in the task context within a block, manipulated by the stimulus set-size in contexts with fewer possible stimuli (4- or 5-item context) or more possible stimuli (8- or 9-item context) from which the memorized content was selected. In the context of fewer possible stimuli, fewer memorized contents from the previous trials interfered with the processing of task-relevant items in the current trial. In the more possible stimuli context, more representations from previous trials interfered with stimulus processing in the current trial.

Figure 1. Across four behavioral experiments, the results revealed that the WM capacity was significantly reduced in the more possible stimuli context relative to the fewer possible stimuli context.
Across four behavioral experiments, the results revealed that the WM capacity was significantly reduced in the more possible stimuli context relative to the fewer possible stimuli context (see Figure 1). Moreover, the reduction in capacity was significant for high WM loads but was not observed when the focus was on only a single item. Together, these findings indicate that context-driven selection history and focused attention influence WM capacity. The findings from this study also provide the intellectual impetus for in-depth work on this essential aspect of human cognition, namely, the manner in which task contexts can proactively affect behavior.

Acknowledgements

This work was supported by the National Taiwan University Cutting Edge Steering Research Project (NTU-CESRP-103R104951).

Deep-sea corals and coral-bioeroding foraminifera in the South China Sea

Coral reefs are shallow-water ecosystems that occur in tropical and subtropical seas. They feature very high biodiversity and primary productivity, as well as beautiful scenery. The species diversity and ecology of the coral reefs bordering Taiwan have been the focus of marine biology studies in the past several decades. However, the biodiversity of deep-sea corals in the seas surrounding Taiwan has not been investigated. From 2013 to 2016, we conducted field surveys on the species diversity and distribution of deep-sea corals in the South China Sea using R/V Ocean Researcher I. In total, 76 localities encompassing Dongsha Atoll, Macclesfield Shoal, and Spratly Island and located at depths ranging from -262 to -3732 m were surveyed. The approximately 8,000 specimens that were collected and examined include 190 species of deep-water scleractinian corals belonging to 15 families and 55 genera, including 1 new genus and 15 new species (Figure 1). Moreover, the species compositions of the coral communities found at the different localities vary widely, indicating that the species diversity of deep-sea corals in the South China Sea is high. Phylogenetic analysis based on two mitochondrial sequences (16S and 28S rRNA) reveals that several cryptic or new species may exist in our collections; thus, the species diversity is likely higher than expected. The high species diversity and the abundance of deep-sea corals found at several localities suggest that deep-sea reefs likely exist in the South China Sea. The calcium carbonate structures formed by deep-sea corals provide essential habitats that promote the survival of fish and invertebrates in marine ecosystems. Based on the high species diversity and the abundance and uniqueness of coral fauna, we propose designating the Dongsha continental shelf, Zhongsha Reef and An-Da Reef in the Spratly Islands as marine protected areas for the conservation of marine resources in the South China Sea.

Among the coral specimens, we found fifteen individuals of Hyrrokkin sarcophaga, a large commensal or parasitic foraminifer, on corals belonging to three species collected at depths ranging from -339 to -552 m. The study reporting this discovery was the first reported occurrence of a coral-bioeroding foraminifer in the Pacific Ocean [1]. H. sarcophaga is a large foraminifer that has tests of up to 7 mm in diameter and is mainly parasitic on deep-sea corals. It has previously been reported as occurring on hexacorals or oc-

Reference


Associate Professor Bo-Cheng Kuo
Department of Psychology
bckuo@ntu.edu.tw
tocrals at depths ranging from -200 to -500 m along the North Atlantic continental margin in polar to subtropical waters [2]; however, it had never previously been reported from the Indian or Pacific Oceans, even after several explorations. In our findings from the South China Sea, three new host corals, i.e., *Madrepora oculata*, *Flabellum japonicum*, and *Caryophyllia diomedeae* (Figure 2), were identified. The boring pattern produced by this large foraminifer characterized by a shallow groove of 0.55 ± 0.04 mm in diameter. Several whip-shaped extensions extend vertically from this groove into the substrate of the host and act as an anchor to enhance the attachment of the foraminifer. These findings extend our knowledge of the global distribution of *H. sarcophaga*, as well as its ecological affinities and host preferences.

References

Professor Chang-Feng Dai
Institute of Oceanography
corallab@ntu.edu.tw

Figure 1. Examples of deep-sea corals.
Figure 2. Deep-sea corals and coral-bioeroding foraminifera
Deep-sea ecosystem functions linked to biodiversity over the past 20,000 years

Biodiversity-ecosystem function (BEF) relationships have received much attention from ecologists, conservation biologists, and managers because they can be used to infer the consequences of losses of biodiversity on earth. Such losses are occurring rapidly due to biomass exploitation, habitat degradation, and especially global climate change. Since the mid-1990s, hundreds of experiments have manipulated the richness of plant or animal species or different combinations of functional groups in the laboratory and in the field to study the response of their ecosystem functions (e.g., biomass production and nutrient cycling) to changes in biodiversity. These experiments have reached a consensus and indicate positive and saturating responses of ecosystem functions to biodiversity. These results imply the importance of maintaining biological diversity and thus the functions and services of ecosystems (e.g., food production and climate regulation). Although much has been learned from these present-day, short-term manipulative experiments, information on how ecosystem functions react to long-term changes in biodiversity is still lacking. The logistical difficulties involved in maintaining long-term ecological monitoring represent the primary challenge in obtaining this information. Nevertheless, such understanding has become more important than ever because the earth’s ecosystems and biodiversity are undergoing long-term degradation by human activities and climate change.

To understand long-term BEF relationships, Dr. Wei and his collaborators analyzed fossil records of microscopic deep-sea crustaceans called ostracodes. These records were obtained from the North Atlantic Ocean and cover the last 20,000 years. Due to the relatively continuous sedimentation that occurs in the deep sea, these records contain excellently preserved calcareous shells of fossil ostracodes and yield chronological information. To provide a link to present-day BEF relationships, Dr. Wei and his collaborators compared the fossil ostracode data to a decadal-long census of deep-sea nematodes in the Mediterranean Sea. Nematodes are the most abundant metazoan invertebrates in the ocean, and they are also one of the most diverse taxa; the ocean is estimated to contain ~4,000 known species. They are tiny and have short generation times and high metabolic rates; thus, they process considerable amounts of energy through their growth and respiration. Both ostracodes and nematodes have well-developed functional traits, including their vertical position on the seafloor, feeding type, mobility, and morphology, and thus reflect additional aspects of biological diversity.

Figure 1. Microscopic views of deep-sea. (A) ostracodes and (B) nematodes. Image credits: Moriaki Yasuhara (University of Hong Kong), Jian-Xiang Liao (National Taiwan University).
The researchers used nematode biomass and the accumulation rate of ostracodes as proxies for ecosystem functions (e.g., productivity in an ecosystem). They compared the taxonomic and functional diversity of nematodes and ostracodes with these proxies of ecosystem functioning to investigate BEF relationships over decadal to millennial time scales and found generally positive, long-term relationships between biodiversity and ecosystem functioning, consistent with studies of BEF relationships based on present-day spatial analyses and short-term manipulative experiments. However, the deep-sea BEF relationships over longer time scales are much noisier than those inferred by modern observational studies. These relatively noisy BEF relationships suggest that environmental changes over decadal to millennial time scales may affect biodiversity and biomass independently, and these effects may be much stronger than the impacts of biodiversity on ecosystem functioning. This study suggests that abiotic factors are more important than biotic factors in shaping the patterns of biodiversity and ecosystem functions at macroevolutionary time scales due to the changes observed over the decadal to millennial time scales investigated in this study are much shorter than the approximate lifespan of a species (1–2 million years). This work also implies that climate change may affect both diversity and ecosystem functioning over long time scales in the deep sea.

Reference

Assistant Professor Chih-Lin Wei
Institute of Oceanography
clwei@ntu.edu.tw

Quantum topological Hall effect in noncoplanar antiferromagnetic oxides

The integer quantum Hall (IQH) effect, first discovered in 1980 by von Klitzing [1] (a 1985 Nobel Laureate), is one of the most fascinating discoveries in physics. When a strong perpendicular magnetic field is applied to a two-dimensional (2D) electron gas (EG) at low temperatures, the Hall conductance is precisely quantized due to Landau-level quantization, and its values are an integer (NC) multiple of the fundamental conductance quantum (e²/h). In 1982, Thouless (a 2016 Nobel Laureate) demonstrated that this quantization is directly connected to the topological property of the 2D bulk insulating states, characterized by a topological invariant called the Chern number (NC) [2]. Intriguingly, the conductance quantum number (NC) is exactly equal to the number (NC) of dissipationless chiral edge states in the 2DEG plane [Figure 1(a)]. The topological interpretation of the IQH effect implies that the effect can also occur in other time-reversal symmetry broken systems with a topologically non-trivial band structure in the absence of the external magnetic field, such as ferromagnetic topological insulators, leading to the so-called quantum anomalous Hall (QAH) effect [Figure 1(b)], as first proposed for a honeycomb lattice model in 1988 by Haldane [3] (2016 Nobel Laureate).

Due to its intriguing nontrivial topological properties and the potential application of its dissipationless edge states for designing low-power consumption electronics and spintronics, extensive studies have been performed to search for real materials to host the QAH effect. Indeed, this extensive effort culminated in the experimental observation of the QAH effect in Cr-doped (Bi,Sb)₂Te₃ ferromagnetic topological insulator films in 2013 by Xue and coworkers [4]. Nevertheless, the QAH phase appeared at extremely low temperatures (less than 30 mK) due to the small band gap, weak magnetic coupling and low carrier mobility. These factors hinder
further exploration of the exotic properties of the QAH phase and its applications.

The problems with weak magnetic coupling and small band gap could be overcome by adopting 4\textit{d} and 5\textit{d} transition metal atoms, which simultaneously have more extended \textit{d}-orbitals and stronger relativistic spin-orbit coupling (SOC). Therefore, through \textit{ab initio} density functional calculations, we have recently conducted a systematic search for high-temperature QAH phases in 4\textit{d} and 5\textit{d} transition metal oxides. Indeed, we discovered that layered rhodium oxide $K_{1/2}$RhO$_2$ in the noncoplanar antiferromagnetic state is a QAH insulator with a large band gap of $\sim$0.2 eV and a Néel temperature of a few tens of Kelvins [5] [Figure 2]. Furthermore, this QAH phase is found to be unconventional because it occurs in the antiferromagnetic state without the need for net magnetization and SOC. The quantum topological Hall effect caused by the nontrivial topology of the noncoplanar antiferromagnetic structure in the system is rather exotic [Figure 2(a)]. These findings thus show that 4\textit{d} and 5\textit{d} metal oxides are promising materials for exploring exotic quantum phases and for realizing advanced technological applications such as low-power consumption nanoelectronics and oxide spintronics.

**References**


Professor Guang-Yu Guo
Department of Physics
gyguo@phys.ntu.edu.tw

---

**Figure 1.** Schematic diagrams of chiral conductive edge states in (a) the integer quantum Hall effect and (b) the quantum anomalous Hall effect. Note that the bulk regions are nonconductive due to either (a) Landau level quantization by the strong magnetic field ($B_z$) or (b) ferromagnetism ($M_z$) plus the relativistic spin-orbit coupling gap.

**Figure 2.** Layered $K_{1/2}$RhO$_2$. (a) Crystalline and antiferromagnetic structure. (b) Edge band diagram. The gapless chiral edge states are denoted by red and blue lines, and black lines represent the insulating bulk band structure. (c) Illustration of the chiral edge states (orange lines) labelled $a$ and $b$ in (b).
Liquid-core/liquid-cladding optical waveguides offer optically smooth liquid/liquid interfaces to guide light along microfluidic liquid streams with adjustable optical properties. We investigated dielectrophoresis (DEP) on an electromicrofluidic platform to construct reconfigurable liquid-core/liquid-cladding optical waveguides by applying adequate electric fields between parallel plates without the constant liquid supply usually needed for laminar flow in physical microchannels. L-shaped, spiral, and straight stationary waveguides were prepared to investigate light guiding and propagation, whereas moving waveguides were established to perform light switching.

As shown in Figure 1, liquid optical waveguide cores were driven on an electromicrofluidic platform between two parallel plates without physical channel walls. With a sufficient nonuniform electric field, DEP generated surface forces to continuously deform and pump the higher-permittivity liquid (core liquid) along the strong electric field into the region containing the lower-permittivity medium (cladding liquid). Because the core liquid was defined by the electric field instead of by laminar flow along physical microchannels, waveguides with arbitrary two-dimensional shapes were obtained by applying a voltage to Teflon-coated ITO (indium tin oxide) electrodes on the inner surfaces of two parallel glass plates. In the stationary L-shaped waveguide, light was guided into the GBL virtual microchannel core for a total of 27.85 mm via a 90° bend (radius 5 mm) before exiting the light outlet with a cross-sectional area of 100 μm × 100 μm. For the stationary spiral waveguide (cross-sectional area of 100 μm × 100 μm), light was guided into the GBL core...
containing rhodamine 6G (R6G, 1 mM) dye through a series of 90° bends with radii decreasing from 5 mm to 2.5 mm. In the stationary straight waveguide (height 100 μm, width 150 μm), the propagation loss was measured to be 2.09 dB/cm in the GBL with R6G (0.01 mM). To implement the moving L-shaped waveguide, electrowetting and DEP generated a precise GBL droplet and then formed a waveguide core on the electromicrofluidic platform. Upon sequentially applying the appropriate voltage to each of three parallel L-shaped driving electrodes, the GBL waveguide core shifted; the guided light was switched to a speed of up to 0.929 mm/s (switching period 70 ms, switching rate 14.3 Hz) when an adequate electric signal (173.1 \( V_{\text{RMS}} \), 100 kHz) was applied.

The DEP-defined waveguide demonstrated simple fabrication, flexible optical and fluidic pathways, and static core/cladding liquids without flow disturbances. The demonstrated liquid-core/liquid-cladding optical waveguides are ready to be integrated with other microfluidic functionalities and optofluidic components on a single electromicrofluidic platform.

Reference

Professor Shih-Kang Fan
Department of Mechanical Engineering
skfan@fan-tasy.org

A fast-track characterization protocol of spin-orbit torque efficiencies

Spin-orbit coupling is a source of many exotic physical phenomena found in various condensed matter systems; these phenomena, such as the current-induced spin Hall effect (SHE) and the spin-orbit torque (SOT), originate from transition metal-based and emergent material-based magnetic heterostructures. The SHE-induced SOT and its related effects have been widely studied both theoretically and experimentally and demonstrated by harnessing the magnetization dynamics in certain material systems (e.g., Pt-, Ta-, and W-based heterostructures). Therefore, the SOT effect might become a major mechanism for controlling next-generation spintronic devices, such as magnetic random access memory (MRAM)/SOT-
MRAM and spin logic devices.

In recent years, several measurement techniques have been adopted to characterize the current-induced effective fields originating from the SOTs in material systems with perpendicular magnetic anisotropy (PMA). These techniques include harmonic voltage measurements, the spin Hall torque magnetometry of the chiral domain wall, and calibrated current-induced magnetization switching measurements. The goal of all these different approaches is nevertheless the same: To determine the sign and magnitude of the current-induced effective field per current density, \( \chi \), from which the spin Hall efficiency and the spin Hall angle of the system can be further estimated.

In our recent work, in collaboration with Professor Geoffrey Beach’s team at Massachusetts Institute of Technology, we have shown that by measuring the current-induced hysteresis loop shift versus the in-plane bias magnetic field, as shown in Figure 1, the SHE contribution of the current-induced effective field per current density \( \chi_{\text{SHE}} \) can be estimated for transition-metal-based magnetic heterostructures with PMA (Ref. 1). A rough estimation of the Dzyaloshinskii-Moriya interaction effective field \( H_{\text{DMI}} \) can also be achieved by this technique. Furthermore, while applying this method to samples with a wedge-deposited ferromagnetic layer, we observed an extra contribution \( \chi_{\text{Wedged}} \) due to the asymmetric nature of the deposited ferromagnetic layer, as shown in Figure 2. The origin of \( \chi_{\text{Wedged}} \) might be related to the asymmetric depinning process in the ferromagnetic layer during magnetization switching; this process was checked by magneto-optical Kerr microscopy (MOKE). The applicability of this newly proposed characterization method has also been further verified in several recent studies regarding SOTs in nonmagnetic (NM)/ferromagnetic systems. These results indicate the possibility of achieving deterministic field-free spin-orbit torque switching by controlling the symmetry of the domain expansion, which will be beneficial for the development of next-generation SOT-MRAM devices. Our method also provides a fast-track and non-invasive method for SOT efficiency determination.

Reference

Assistant Professor Chi-Feng Pai
Department of Materials Science and Engineering
cfpai@ntu.edu.tw

Figure 2. (a) Schematics of the wedge-deposited ferromagnetic layer (cobalt (Co) in this case) sample. (b) Extracted SOT efficiencies from the wedged sample. The contributions from the structural effect \( \chi_{\text{Wedged}} \) and the spin Hall effect \( \chi_{\text{SHE}} \) can be easily deciphered. (c) The relative strengths of the two SOT contributions. (d) The MOKE-obtained switching dynamics for the uniformly deposited and wedge-deposited samples, which indicate different switching modes. (Reproduced from Ref. 1)
A novel mechanism of fine-tuning inflammatory responses

Inflammation is an important component of innate immunity and is quickly induced by the host upon pathogenic infection. Upon infection, innate immune cells, such as macrophages, use pattern-recognition receptors (PRRs), mainly Toll-like receptors (TLRs), to detect conserved microbial molecules termed pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) released from injured or dead cells. Then, innate immune cells mount a defensive response to clear pathogens or damaged cells and coordinate the adaptive immune response. However, the innate immune response must be spatially and temporally controlled to avoid excessive inflammation.

Among PRRs, TLR4 plays a central role in the recognition of both Gram-negative and Gram-positive bacteria. Upon TLR4 engagement, a serial of protein kinase cascades, including IκB kinase (IKK) and mitogen-activated protein kinase (MAPK), are activated to induce the production of pro-inflammatory cytokines, chemokines, and type I interferons. However, despite extensive investigation, the regulation of TLR4-mediated inflammatory responses remains unclear.

A research group led by Dr. Li-Chung Hsu at the Institute of Molecular Medicine has been focused on studying the regulation of innate immunity and host responses against pathogenic infection and tissue damage. Hsu’s group recently identified an E3 ubiquitin ligase, ZNRF1, that modulates Caveolin-1 (CAV1, the major constituent of caveolae) ubiquitination and degradation, leading to regulation of TLR4-triggered inflammatory responses. Consistently, mice with deletion of ZNRF1 in their hematopoietic cells display increased resistance to endotoxic and polymicrobial septic shock due to attenuated inflammation. Mechanistically, ZNRF1-modulated CAV1 expression regulates Akt-GSK3β signaling; the downstream targets of this pathway inhibit inflammatory responses by suppressing induction of pro-inflammatory cytokines and enhancing production of anti-inflammatory cytokine IL-10. This study demonstrates that TLR4 activation induces a transient association between CAV1 and ZNRF1 as well as a decrease in CAV1 protein levels through the ubiquitin/proteasomal pathway to allow the inflammatory response to quickly shift toward pro-inflammatory cytokine/chemokine production. This shift is needed to constrain pathogens during the early phase of host infection.

Sepsis caused by uncontrolled inflammation is the leading cause of death in intensive care units today. Numerous efforts have been made to develop therapeutic agents to block massive inflammation in septic patients, but these efforts have not yielded much success. In addition, chronic inflammation is mechanistically linked to numerous human diseases, including cancer and diabetes. Therefore, understanding the molecular mechanism of regulation of innate immunity has far reaching implications for the study of inflammation, cancer and infectious diseases. The study by Hsu’s group indicates that ZNRF1 is a novel regulator of TLR4-driven inflammation through controlling CAV1 protein levels. Moreover, excessive CAV1 expression has been shown to contribute to a variety of human diseases, including cancer metastasis and atherosclerosis. Thus, this finding suggests a novel therapeutic target for treatment of inflammatory and CAV1-related diseases.

Reference
Chih-Yuan Lee, Ting-Yu Lai, Meng-Kun Tsai, Yung-Chi Chang, Yu-Hsin Ho, I-Shing Yu, Tzu-Wen Yeh, Chih-Chang Chou, You-Sheng Lin, Toby Lawrence, and Li-Chung Hsu (2017). The Ubiquitin Ligase ZNRF1 promotes caveolin-1 ubiquitination and degradation to modulate inflammation. Nature Communications, 8, 15502. DOI: 10.1038/ncomms15502

Associate Professor
Li-Chung Hsu
Institute of Molecular Medicine
College of Medicine
lichunghsu@ntu.edu.tw

Clinical Assistant Professor
Chih-Yuan Lee
Department of Surgery
National Taiwan University Hospital
gs2119@yahoo.com.tw
Snake venom is a key ingredient for developing anti-thrombotic agents

Upon vessel wall injury, the integrity of the endothelial cell layer is disrupted, and platelets interact with exposed extracellular matrix (ECM) molecules. The initial interaction between platelets and subendothelial collagens under high-shear conditions is indirectly mediated by a plasma protein, von Willebrand factor (vWF), which binds collagen and the platelet glycoprotein (GP) Ib/V/IX complex. This unstable interaction facilitates transient platelet tethering and rolling on the injured endothelial cells. Subsequent firm adhesion is mediated by collagen binding to its platelet receptors, principally integrin α2β1 and GPVI. Recently, elevated platelet GPVI expression was found in acute coronary syndromes, transient ischemic attacks and strokes, indicating that GPVI may serve as a biomarker for acute atherothrombotic events. Using Fab fragments from monoclonal antibodies effectively inhibits collagen-induced platelet aggregation in vitro and ex vivo and during in vivo thrombosis in rats without prolonging the bleeding time. An increasing number of studies imply that blocking collagen from binding to GPVI prevents initial adhesion and further activation of the platelets and has an enormous impact on antithrombotic therapy.

GPVI is an important collagen receptor and an ideal target for snake venom proteins. When GPVI is clustered by ligands, it induces massive platelet activation. Several snake venoms that activate platelets via GPVI have been identified, including trowaglerix from Tropidolaemus wagleri. The partial amino acid sequences of trowaglerix were used to demonstrate that the hexa-/decapeptides of its α subunit specifically exhibited marked inhibitory activity against collagen-induced platelet aggregation by interacting with the GPVI receptor in vitro and effective anti-thrombotic activity in mouse models without causing bleeding. Through computational peptide design and molecular
dynamics simulations of the trowaglerix-based decapeptides and GPVI, a possible binding site was identified near the D1/D2 domain surface, which differs from well-known collagen-binding sites.

To the best of our knowledge, this is the first study to design small-mass peptides derived from snaclecs with anti-thrombotic activity that target the platelet GPVI receptor with an atypical binding epitope. We also demonstrated the in vivo antithrombotic effect of trowaglerix-based decapeptides. Intravenous administration of trowaglerix-based decapeptides delayed thrombus formation and significantly prolonged time-to-occlusion (TTO) in irradiated mesenteric venules of mice pretreated with fluorescein sodium. Prolonged bleeding is a common undesirable side effect of antithrombotic therapy. Trowaglerix-based decapeptides did not noticeably affect the bleeding time in mouse tail transection models. These results provide a promising novel molecular skeleton for designing a new class of anti-thrombotic agents targeting platelet GPVI with limited bleeding side effects.

Since all of the natural ligands of GPVI are proteins, new agents should be developed as peptide modulators that can regulate protein-protein interaction. In addition, peptide drugs possess many advantages, such as high potency and specificity with few toxicological problems. To find better decamer peptides that inhibit GPVI on the collagen-binding site, we developed a greedy algorithm-based peptide-design method (Figure 1). The analysis of the structure-activity relationship will provide valuable information for exploring many facets of platelet function and hemostasis. We will further study the linear peptide, cyclic peptide and small molecule compound to provide new options to further treat arterial thrombogenic diseases.

![Figure 1. The docking scores on the collagen-binding site of GPVI, platelet aggregation inhibition activity of selected decamer peptides from trowaglerix α (A) and the docked pose of peptide LFHVWDYTDR (cyan) on the collagen-binding site of GPVI (B).](image)

**Reference**

**Professor Yufeng J. Tseng**
Graduate Institute of Pharmacology
Department of Computational Science and Information Engineering
yjtseng@csie.ntu.edu.tw

**Professor Tur-Fu Huang**
Graduate Institute of Pharmacology
turfu@ntu.edu.tw
Influence of genetic variants on the response to lithium treatment in bipolar disorder

Bipolar disorder (BPD) is a major psychiatric illness with a chronic recurrent course, ranked among the leading disabling diseases worldwide. Lithium medication remains a first-line treatment option among BPD patients despite varying outcomes in treatment response. About two-thirds of BPD patients do not achieve full remission with lithium treatment. Significant genetic contributions have been suggested to account for part of the inter-individual differences in treatment response. The identification of such differences might allow for a better selection of treatments for BPD patients and facilitate the development of novel treatments for BPD in the future.

The assessment of the response to lithium maintenance treatment in BPD is complicated by variable lengths of treatment, an unpredictable clinical course, and often inconsistent compliance. A rating scale (called the Alda scale) was previously developed to reliably and accurately assess lithium treatment response. Given the particular difficulties in obtaining long-term data of sufficient quality to adequately define treatment response, there is a strong need for groups to work together to jointly assemble and analyze cohorts to obtain replicable findings for follow-up studies. The Alda scale has been validated in an international collaboration network, the Consortium on Lithium Genetics (ConLiGen), for which we contribute as one of the member sites.

A positive lithium response has previously been reported to be associated with several genetic variants, including variations in chromosome 4q32, core clock genes, GRIA2, and GAD1. However, none of these findings have been replicated in other studies. With the joint efforts of 22 international sites with samples from 2563 BPD patients and the use of a standard assessment scale for treatment response in the ConLiGen, we adopted a genome-wide association study design and performed whole-genome pharmacogenetic analyses. We found that a single locus of four linked markers on chromosome 21 met genome-wide significance criteria for association with lithium response (the smallest p-value=3.31×10⁻⁹, Figure 1). This gene has not been previously associated with any treatment response-related traits and is located in a gene transcribing a long non-coding RNA (lncRNA),...
namely, AL157359.3, in this predominantly European sample. In an independent prospective study of 73 patients treated with lithium monotherapy for a period of up to 2 years, we replicated this finding, showing that carriers of the response-associated alleles had a significantly lower rate of relapse than non-carriers.

This is by far the largest genome-wide association study of lithium response in BPD published to date with significant results, and the main finding is an association with a non-protein coding gene. This finding provides some clues for lithium’s mechanism of action in BPD, although replication in large independent samples is preferable. There has been an increasing appreciation of the role of IncRNAs in gene regulation, especially in the central nervous system. Nevertheless, the exact function of the identified loci is unknown. Thus, the clinical importance of these findings might still be limited by insufficient knowledge of the function of this gene and its impact on pharmacokinetics and drug mechanisms. Notably, the identified locus showed no prominent effect on lithium response in samples of Asian ancestry in the ConLiGen (i.e., Japanese and Taiwanese samples). Within the Asian cohort, a different marker in the GFRA2 gene that codes for a glial cell line-derived neurotrophic factor receptor showed a suggestive association (p-value=2.1×10⁻⁷). This marker did not pass quality control in the European samples, indicating the relevance of searching for ethnic group-specific genetic variants. Furthermore, the necessary next step to uncover the underlying mechanisms of lithium treatment will be to test the functions of identified variants in cellular and animal models, eventually leading to better treatment options that benefit clinical patients.

References
3. Liping Hou, Urs Heilbrunner, Franziska Degenhardt, Mazda Adli, Kazufumi Akiyama, Nirmala Akula, Raffaella Ardau, Bárbara Arias, Lena Backlund, Claudio E M Banzato, Antoni Benabarre, Susanne Bengesser, Abesh Kumar Bhattacharjee, Joanna M. Biernacka, Armin Birner, Clara Brichtant-Petitjean, Elise T. Bui, Pablo Cervantes, Guo-Bo Chen, Hsi-Chung Chen, Caterina Chillotti, Sven Cichon, Scott R. Clark, Francesc Colom, David A. Cousins, Cristina Cruceanu, Piotr M. Czerski, Clarissa R. Dantas, Alexandre Dayer, Bruno Étain, Peter Falkai, Andreas J. Forstner, Louise Frisén, Janice M. Fullerton, Sébastien Gard, Julie S. Garnham, Fernando S. Goes, Paul Grof, Oliver Gruber, Ryota Hashimoto, Joanna Hauser, Stefan Herm, Per Hoffmann, Andrea Hofmann, Stephane Jamain, Esther Jiménez, Jean-Pierre Kahn, Layla Kassem, Sarah Kittel-Schneider, Sebastian Kliwicki, Barbara König, Ichiro Kusumi, Nina Lackner, Gonzalo Laje, Mikael Landén, Catharina Lavebratt, Marion Leboyer, Susan G. Leckband, Carlos A López Jaramillo, Glenda Macqueen, Mirko Manchia, Lina Martinsson, Manuel Mattheisen, Michael J. McCarthy, Paul Grof, Oliver Gruber, Ryota Hashimoto, Joanna Hauser, Stefan Herm, Per Hoffmann, Andrea Hofmann, Stephane Jamain, Esther Jiménez, Jean-Pierre Kahn, Layla Kassem, Sarah Kittel-Schneider, Sebastian Kliwicki, Barbara König, Ichiro Kusumi, Nina Lackner, Gonzalo Laje, Mikael Landén, Catharina Lavebratt, Marion Leboyer, Susan G. Leckband, Carlos A López Jaramillo, Glenda Macqueen, Mirko Manchia, Lina Martinsson, Manuel Mattheisen, Michael J. McCarthy,
The R&D premium and takeover risk

Why do firms with high R&D intensity offer their investors higher stock returns? Although R&D typically has long-term implications for future earnings, its costs must be expensed as they occur and could therefore negatively impact reported earnings. Certain studies suggest that R&D expensing can lead to earnings distortion and mispricing, whereas other investigations argue that uncertainty about R&D outcomes may generate additional risk, leading investors to require higher returns. Our study offers a new perspective on the R&D premium. We hypothesize that a firm’s probability of becoming a takeover target increases with its R&D intensity and that takeover probability affects the pricing of its common stock.

Prior papers have shown that firms invest in R&D to increase their appeal as takeover targets since takeovers generate huge premiums for target shareholders. Moreover, Chan, Lakonishok, and Sougiannis (2001) demonstrate that firms with high R&D intensity typically have beaten-down stocks. Therefore, for potential acquirers in need of R&D capacity to generate growth, high R&D capacity relative to firm valuation makes R&D-intensive firms attractive takeover targets. Therefore, we hypothesize that R&D-intensive firms are more sensitive to shifts in takeover waves and face higher takeover risk, a systematic risk proposed by Cremers, Nair, and John (2009). They suggest that the values of firms that are more likely to become takeover targets will increase more when economic fundamentals are good and acquirers are flush with cash to pursue takeovers. Conversely, as a takeover wave recedes, the values of firms with higher takeover probabilities will exhibit greater declines. Thus, the values of firms facing higher takeover probabilities will fluctuate with the crests and troughs of takeover waves. Cremers et al. (2009) construct a takeover factor to capture takeover waves and use the sensitivity of a firm’s stock returns to the takeover factor to measure the firm’s takeover risk.

We find robust evidence that a firm’s R&D intensity is a significant determinant of its likelihood of becoming a takeover target, with higher R&D intensity associated with higher takeover probability. Moreover, Fama-MacBeth regressions reveal a positive relationship between the R&D premium and takeover probability even after controlling for many R&D-related factors. Furthermore, we confirm the well-known fact that the R&D premium is large, approximately 2.81 percent per month, during months when the takeover factor is positive.

Dr. Hsi-Chung Chen
Department of Psychiatry & Center of Sleep Disorders, National Taiwan University Hospital
hsichungchen@ntu.edu.tw

Professor Po-Hsiu Kuo
Institute of Epidemiology and Preventive Medicine
phkuo@ntu.edu.tw
as indicated in Figure 1. However, the R&D premium is significantly negative, approximately -1.37 percent per month, during months when the takeover factor is negative. Our findings suggest strong co-movement of the R&D premium and the takeover factor and illustrate a major risk of holding highly R&D-intensive firms’ stocks when the takeover factor falters, which typically occurs as takeover waves recede.

Two other anomalies related to R&D have also been noted in the literature: (i) the premium associated with large R&D increases documented by Eberhart, Maxwell, and Siddique (2004) and (ii) the innovation efficiency premium documented by Hirshleifer, Hsu, and Li (2013). Can takeover risk also help explain these two R&D-related anomalies? Interestingly, we find that similarly to R&D-intensive firms, firms with large R&D increases have an increased likelihood of becoming takeover targets. However, we find that a firm’s innovation efficiency, as measured by its patent citations divided by its R&D investments, is not related to its likelihood of becoming a takeover target. This result is unsurprising given Bena and Li’s (2013) finding that firms with large patent portfolios and low R&D expenses tend to be acquirers rather than takeover targets. Consequently, we expect and find that takeover risk is not responsible for abnormal returns associated with innovation efficiency.

References

Professor Yanzhi Wang
Department of Finance
yzwang@ntu.edu.tw

Figure 1. Premiums Sorted by the Sign of Takeover Factor Returns
Faculty Positions Open

School of Veterinary Medicine

<table>
<thead>
<tr>
<th>DEADLINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 20, 2018</td>
</tr>
</tbody>
</table>

Institute of Applied Mechanics

<table>
<thead>
<tr>
<th>DEADLINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 30, 2018</td>
</tr>
<tr>
<td>September 30, 2018</td>
</tr>
<tr>
<td>December 31, 2018</td>
</tr>
<tr>
<td>February 28, 2019</td>
</tr>
</tbody>
</table>
NTU Plus Academy programs enable students from all over the world to gain experience, university credits, and cultural exploration—all within an international setting based on academic and personal growth. NTU Research programs give students the tools to succeed in diverse environments by encouraging innovative research and hands-on experience in various fields of study.
The "Ginkgo Bridge", which was built in the River-Head area (溪頭), was designed by the fourth-grade Civil Engineering students in National Taiwan University. This project is a great improvement in Taiwan cooperated by the Forest Department, the Civil Engineering Department, the professional architectures and structure engineers. Ginkgo Bridge was inspired by leaf shape of ginkgo which was planted around the site. It connected the ginkgo forest and the university, providing tourists with different view on the river. Ginkgo Bridge was the first project in the Civil Engineering Department that students' design turned into real project with the help from professional. It is also a milestone of the stone-related courses in the department which provides more possibility for future students.