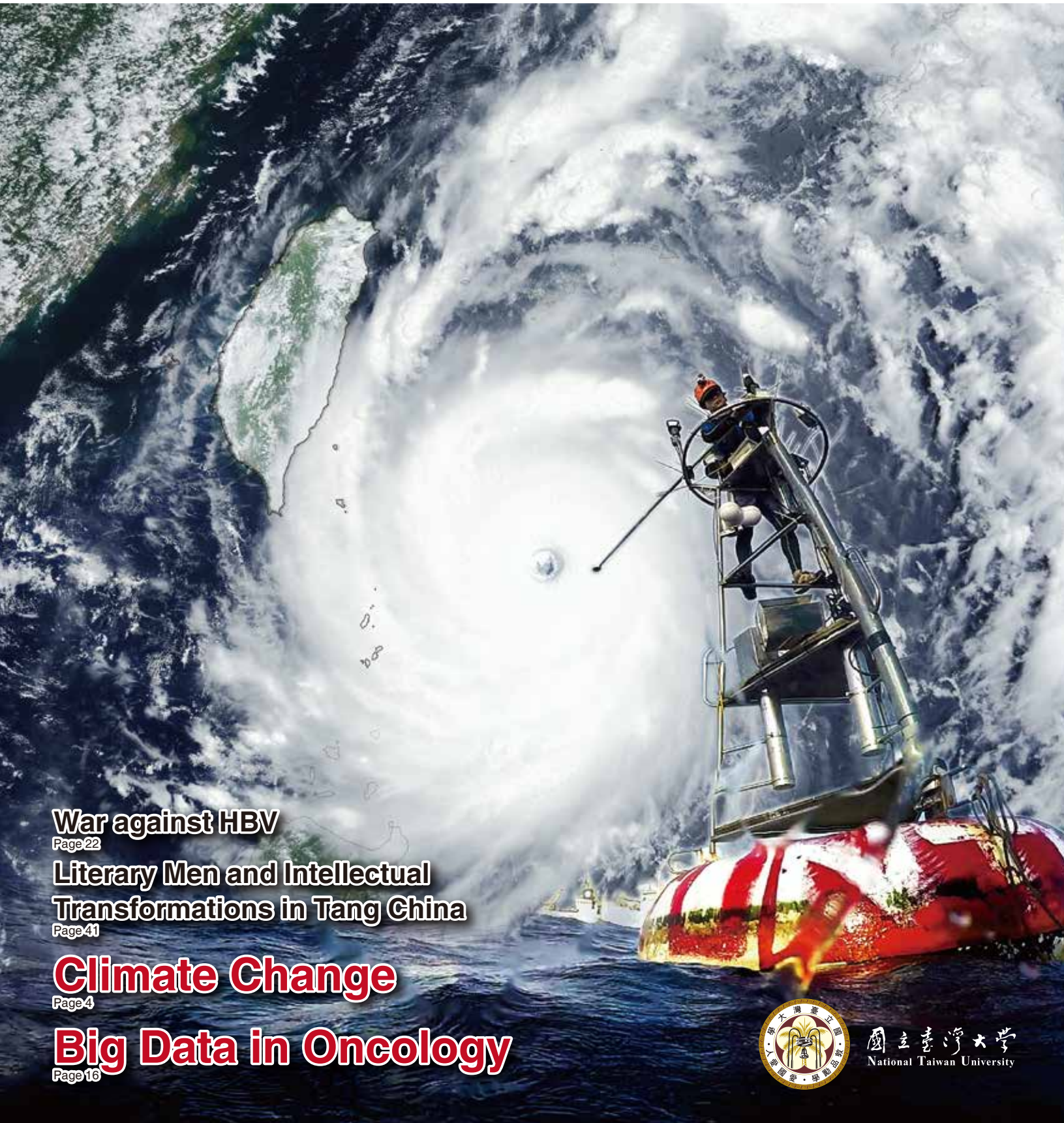
LANDSCAPE

NTU RESEARCH AND DEVELOPMENT

Issue 2 January 2017



國立臺灣大學
National Taiwan University

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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.

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http://www.ntu.edu.tw/spotlight/spotlight.html
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ISSN 2518-4326 (printed version)
ISSN 2519-6502 = Landscape (Taipei. Online)
GPN 2010501304

Editorial Notes

This issue of Landscape covers several topics. In addition to the cover story on climate change, we present a special feature on big data analytics in cancer research and drug prescriptions. Global prescriptions of fluoroquinolone antibiotics have increased from 4.75 billion units to 7.81 billion units between 2000 and 2010. Fluoroquinolone is widely used to treat bacterial infections in the respiratory tract, intra-abdominal organs, eyes, skin structural components, and genitourinary tract. Using big data from the National Health Insurance Database, a National Taiwan University (NTU) team discovered a nearly 3-fold increase in the risk of aortic aneurysms and dissections in patients administered fluoroquinolone. These findings provide important new insights into global drug safety.

NTU is the most comprehensive university in Taiwan, and our researchers have authored articles and books in the fields of medicine, public health, life sciences, arts and humanities, social sciences, engineering, and mathematical and physical sciences. Several articles in medicine and public health are worthy of notice. An estimated 240 million people worldwide have chronic hepatitis B virus (HBV) infection. One article presents an interview with researchers who conducted a study to unravel the mystery of age-dependent immunity against HBV. In the study, experiments were conducted on mice of different ages, and the results supported the hypothesis that the microbiota plays a crucial role in liver immunity against HBV. Another article reports that the risk of gastric cancer may be reduced by Helicobacter pylori eradication, and the findings provide strong clinical support for a mass eradication program to reduce gastric cancer worldwide. Finally, this issue also includes an article that examined how stress can initiate drug relapse. Drug relapse can be induced by environmental factors and stress, even after extended periods of time, and such relapses can lead to the failure of drug rehabilitation programs. The results provide important insights for the development of OX1R antagonists as a novel therapeutic approach in the prevention of stress-related cocaine relapse.

In the life sciences, NTU entomologists collaborated with a Japanese natural history museum to discover a new species of solider beetle in Taiwan. This discovery lends credence to the hypothesis that the plasticity of a species' life span is essentially caused by physiological interpretations of the sensory environment in which the animal lives. History is also an important discipline at NTU, and Professor Jo-shui Chen's book, "Literary Men and Intellectual Transformations in Tang China" sheds light on important intellectual arguments from tenth- to early-eleventh-century in China. This issue of Landscape includes many other fascinating articles and abstracts of published articles and books that provide a quick glimpse into the high-quality research conducted at NTU. It is our sincere hope that you enjoy reading them.

Hung-Chi Kuo

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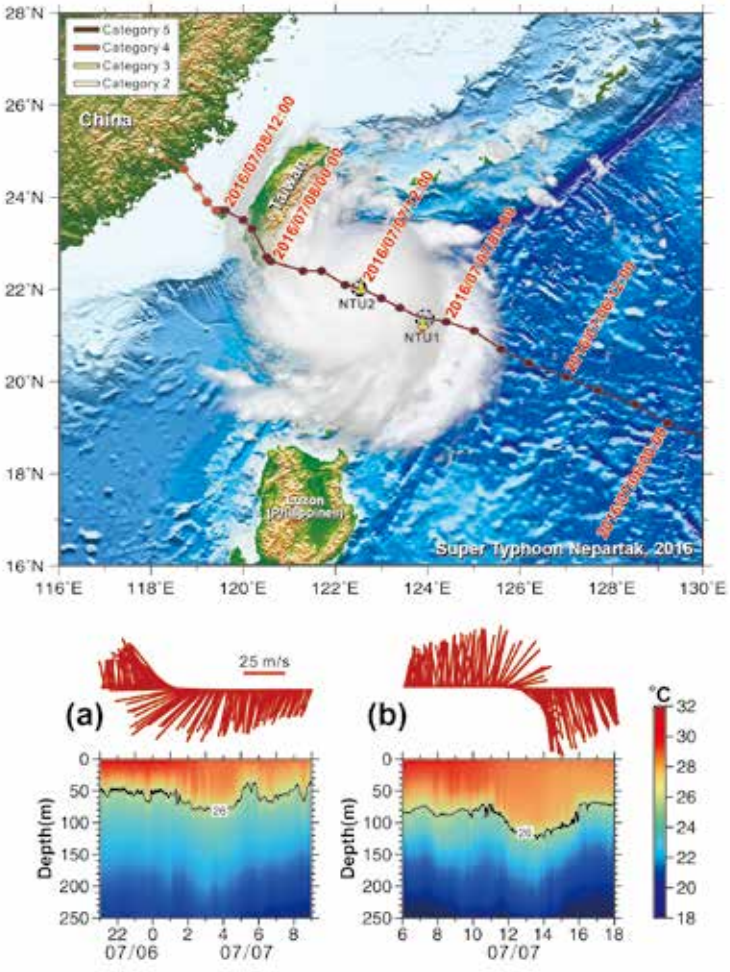
Cover Story



Typhoon Nepartak captured by satellite Himawari-8 at 2016/07/07/02:30 and 2016/07/07/12:00 UTC (available at http://himawari8.nict.go.jp/). Typhoon track is shown and buoy measured wind velocities and seawater temperatures in the upper 250 m are also shown at (a) NTU1 from 2016/07/06/21:00 to 2016/07/07/09:00, and (b) NTU2 from 2016/07/07/06:00 to 2016/07/07/18:00.

On July 6, 2016, NTU1's atmospheric and oceanic sensors picked up important data from Typhoon Nepartak. The data revealed that the storm had an air pressure of about 940 hPa, a maximum wind gust of 41 m/s (~148 km/h or ~82 knots), and that it produced a drop in seawater temperature from 31°C to 28°C in the depths of the ocean's upper 100 m.

As Nepartak raged on and approached NTU2, the second buoy recorded a surprisingly low air pressure of about 911 hPa and a maximum wind gust of 44 m/s (~158 km/h or ~88 knots). In addition, the seawater in the upper 120 m was stirred vertically by the fierce winds. The precious and abundant in situ atmospheric and oceanic data that were collected by the two buoys and that were transmitted back to the Institute in a real-time manner must help to improve the timeliness and accuracy of typhoon forecasting.

The buoys, NTU1 and NTU2, were moored about 375 km and 175 km, respectively, from the southernmost tip of Taiwan. These locations were chosen because they lay in the path or track that a typhoon would most likely take, as predicted by analysis of data pertaining to previous typhoons from prior, strong El Niño years.

The two buoys are the second generation of environment-observing and data-capturing devices which have been developed and improved upon since early 2015 by a research team led by Institute of Oceanography Director Ching-Ling Wei (魏慶琳) and Associate Professor Yiing-Jang Yang (楊穎堅). The air-sea observation buoys were deployed from the research vessel R/V Ocean Researcher I into the western North Pacific in late June of 2016 as part of the team's long-term project to observe typhoons directly from the ocean.

Additional information available at https://eos.org/project-updates/new-data-buoys-watch-typhoons-from-within-the-storm

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Reference

Sen Jan, Yiing Jang Yang, Hung-I Chang, Ming-Huei Chang, and Ching-Ling Wei. (2017). New data buoys watch typhoons from within the storm. *Eos*, 98. DOI: https://doi.org/10.1029/2017EO069821. Published on 27 March 2017.

Contents

Introduction to climate change governance and law

From the Kyoto Protocol to the Paris Agreement: Climate Change 2.0

The year 2016 saw two surprising events in the world of climate change governance. First, the Paris Agreement was ratified by more than 55 state parties, which together account for more than 55% of the world's greenhouse gas emissions, on October 5, and it officially became effective on November 4. Second, Donald Trump, a climate change skeptic, was elected as President of the United States, one of the largest greenhouse gas-emitting countries. As glaciers have melted down at unprecedented speed, sea levels have risen, and the frequency of extreme weather has increased, climate change and its adverse impacts have changed the ways in which people live and influenced how governments at all levels govern and enforce laws. The global community has come to the realization that climate change is no longer a purely scientific concern. Prompt action must be taken, and we must adapt to ever-changing circumstances.

State-centric negotiation and its limitations

Prof. Yeh clearly notes in Climate Change Governance and Law (National Taiwan University Press, 2015) that "state-centric negotiation" is the main obstacle that prevents nation states from reaching consensus in combating climate change. The large-scale and cross-border impacts of climate change make sovereignty-based international negotiations seem infeasible. The confrontation between developed and developing countries also deadlocked when the Kyoto Protocol placed a heavier burden on developed nations under the principle of "common but differentiated responsibilities". Powerful nation states dominate major negotiations at the Conference of Parties (COP) of the United Nations Framework Convention on Climate Change (UNFCCC). Procedural malfunctioning has also worsened the negotiation process. Lack of transparency, participatory mechanisms and clear rules for decision-making processes are hurdles to effective participation for all climate change stakeholders. State-centric negotiations and procedural malfunctioning have led to disappointing results in international negotiations, as at COP 15, held in Copenhagen in 2009, where no consensus on a legally binding instrument for the post-Kyoto era was reached.

Breaking through: Multi-level governance and governability

In the context of climate change, the boundaries between nations have become blurred, and state sovereignty has been eroded. Accordingly, Prof. Yeh points to multi-level governance, a more holistic approach to adapting to climate change. Climate change cannot be circumscribed by a nation or an administrative district. Taking a bottom-up approach, supra-state organizations actively participate in climate governance. For example, the European Union (EU) integrated its member states into corresponding legal and policy frameworks and requested that every member state comply with the EU standard. Meanwhile, the EU still plays a critical role in international negotiations, as seen in its support for the establishment of the first Emissions Trading System Market in the world. Also following the bottom-up approach, sub-state entities have also actively participated in climate change governance. Cities on the front lines of combatting climate change began to be formally recognized at COP 21, held in 2015 in Paris. ICLEI - Local Governments for Sustainability, the most prominent association of cities and communities, shattered the conventional wisdom that only nation states could play an important role in international legal governance. At COP 22, held in 2016 in Mar-

rakech, cities, towns and regions were all represented. Now, in many places, emission reduction efforts are led by cities that have played a prominent role in helping nation states to achieve their National Determined Contributions (NDCs). Non-governmental organizations and elements of the private sector are all fully involved in this global issue and are willing to take on the tasks it requires. Climate change governance is a classic example of the challenge of global administrative law. Diverse regulatory sources and institutions are created, and multilevel cooperation and interaction are developed. Accountability is ensured through the establishment of compliance and supervisory mechanisms. The NDCs enacted in the Paris Agreement reflect the trend in global administrative governance in which every party state considers its own situation when setting its mitigation, adaptation, funding and technology goals. Every five years, there will be a global stocktake to assess collective progress towards achieving the ultimate purpose of the Agreement and to inform further actions by state parties.

Policy instruments, target issues and norms

Under the concept of multilevel governance, Prof. Yeh presents various policy instruments, including market mechanisms, economic incentives and innovative solutions to the attribution and distribution of climate change liability among states. The current climate change regime has failed to develop a decent solution to the attribution and distribution of state liability. Prof. Yeh proposes the creation of a global climate change liability fund, in which the obligatory share of each state is, first, to be benchmarked by its contribution to historical cumulative emissions and, second, must also reflect present emission dynamics. In the next part, six targeted issues including energy, adaptation, finance, trade, human rights and hazard prevention are addressed and examined to determine whether the relevant policy instruments are capable of tackling them. From the legislative framework perspective, Prof. Yeh reviews climate change legislation worldwide and suggests a possible framework for Taiwan.

Taiwan's adaptation under climate change governance

As a major greenhouse gas emitter, Taiwan is also highly vulnerable to climate change. Prof. Yeh believes that multi-level governance provides an alternative through which Taiwan – often isolated from state-centric international negotiations – can participate in the international community. A global city like Taipei has a better chance of engaging in discussions on international climate change governance by participating in the ICLEI, joining the world carbon trade markets and communicating with the international community about adaptation technology. Meanwhile, its vibrant civil society and non-governmental and non-profit organizations can actively engage in international initiatives.

In recent years, environmental legislation in Taiwan has made significant progress. The Greenhouse Gas Reduction and Management Act was passed in July 2015, and three land management acts were passed consecutively: the Wetland Conservation Act in 2013, the Coastal Zone Management Act in 2015, and the National Land (Spatial Planning) Act in 2016. This is a critical moment for Taiwan to establish a climate change adaptation plan and promptly reshape the current landscape of climate change law and policies. Taiwan's strategy must not emulate traditional ideas or conventional wisdom. Rather, it must identify new trends and use innovative legal thinking to meet the unprecedented challenge of climate change, now and in the coming centuries.

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Jiunn-rong Yeh. (2015). *Climate Change Governance and Law*. Taipei: National Taiwan University Press.

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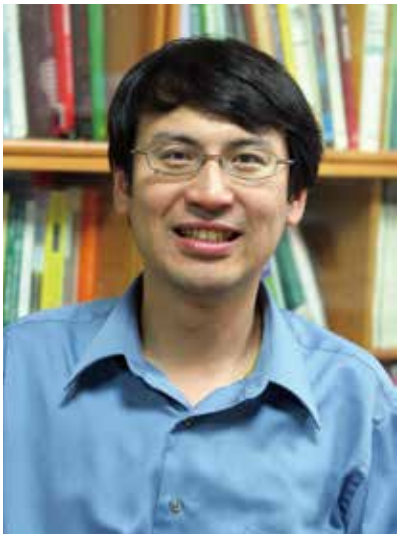
The barriers and challenges of urban climate governance in Taiwan

A multilevel governance perspective



The role of cities in climate governance

Urban climate governance has become a vital aspect of contemporary global governance. In 1976, when the United Nations held the first UN-Habitat in Vancouver, Canada, two-thirds of the world population was concentrated in rural areas. Now, forty years later, half of the world population lives in cities, and fast-paced urbanization has created grand challenges for urban governance systems. Since the industrial revolution, developing economic and social activities have resulted in the heavy use of fossil fuels for energy, causing the concentration of anthropogenic greenhouse gases in the atmosphere to skyrocket and gradually increasing global average temperatures. The IPCC's 5th Evaluation Report (2013) estimated that by the end of the 21st century the global average temperature will rise by 1.8-4.8°C; already, urban energy consumption accounts for more than 70% of the world's energy consumption. Global climate change drives the need for a low-carbon economy and a social transition accompanied by changes in the social structure together with the rapid development of cities, thus creating challenges for human economic activities, the environment and political structures.

Climate change issues span the boundaries of "global commons" and "multilevel." Although globalization has become the driving power of global political and economic structures, from an analytical perspective globalization cannot explain the complicated mechanisms within a country, especially the role of subnational authorities such as local governments and cities in global issues. In December 2007, COP 13, held by the UNFCCC in Bali, Indonesia, and the World Mayors Council on Climate Change actively proposed a 60% reduction in greenhouse gas emissions by 2050 compared to the level in 1990, and an 80% reduction was proposed for industrializing countries for the same period. City mayors promised to draft local-level strategies of mitigation and adaptation. Through international connections, urban networks are likely to become the main force behind post-Kyoto global climate strategies.

The main concern of this study is to probe the barriers and challenges of climate governance faced by cities in Taiwan. By 2014, the author of this study had conducted in-depth interviews with 26 officials, including 13 commissioners and deputy commissioners in related bureaus from each city, central government bureaucrats, scholars, experts and NGO representatives. The interviews focused on aspects of multilevel governance, such as horizontal and vertical governance, as well as climate change-related policies, governance strategies, governance predicaments and challenges faced by each city. This paper discusses the current challenges of global climate governance and reviews the climate policy development of Taiwan's central and local governments. Finally, the barriers and challenges of urban climate governance in Taiwan are analyzed from a multilevel perspective.

Barriers and challenges of urban climate governance

This study investigates the barriers and challenges faced by Taiwanese cities to clarify how, under Taiwanese political and social structures, cities and local governments respond to climate problems. With respect to climate change mitigation or adaptation strategies, the uncertain position of central governmental policy was the main problem facing Taiwanese cities. Under the cen-

tralized system of the Taiwanese government, the responsibilities of local governments are often difficult to determine. Given the long-delayed enactment of the Greenhouse Gas Reduction and Management Act, which was not passed until 2015, the action programs of the central government are limited and cannot provide an integrated response to the impact of climate change. Several Taiwanese cities have attempted but failed to collect a carbon tax or congestion fee to complement local financial resources and reduce carbon emissions due to the vagueness of the roles and responsibilities of local governments.

Currently, the main legal structure regarding the climate change issue are generally known as the Four Laws of Energy and Carbon Reduction, which include Greenhouse Gas Reduction and Management Act, Renewable Energy Development Act, Energy Management Act, and Energy Tax Act (under discussion). In addition to mitigation strategies, the "Adaptation Strategy to Climate Change in Taiwan" has been published in 2012 as a national policy framework for adaptation strategies and actions. The policy framework identifies 8 sectors to evaluate climate impacts and challenges, which includes disasters, infrastructure, water resources, land use, costal zones, energy supply and industry, agriculture production and biodiversity, and health. However, there has been a gap in coordinating the mitigation and adaptation strategies and actions in terms of organizational mechanism.

This study also finds the funding problem in policy implementation, which occurs primarily because Taiwanese local governments lack sufficient financial bases. Since local financial resources are insufficient for implementing climate policies, the role of the central government and subsidies for local governments becomes critical in the realization of local climate policy.

Local governments frequently encounter a gap between scientific information and local knowledge. Cities with insufficient financial resources and manpower often do not have adequate information regarding the local climate to establish regulations in accordance with local conditions and to offer appropriate direction for climate adaptation strategies.

In essence, the Taiwanese response to climate change is mainly voluntarism—namely, low-carbon city strategies based on international trends regarding carbon reduction and energy transition. Although some evidence indicates that cities have both advantages and responsibilities in addressing climate issues, this study finds many restrictions within existing structures and social values. These restrictions create both new opportunities and challenges for urban climate actions given the increasing acknowledgment of climate change and unfolding of policy directions of Taiwanese cities.

In evaluating the development of climate policy in Taiwan's main cities in recent years, we find that except for the pioneering cities of Taipei City, New Taipei City and Kaohsiung City, most cities have followed the policy of the central government and have put forth educational and promotional strategies as their main approach. As the issue of urban climate governance gradually unfolds, local governments choosing policy instruments risk collision with existing structures, reflecting the predicament and challenges of multilevel governance that cities face. For example, insufficient local financial resources restrict opportunities for local governments to use distributive policies such as subsidies. Additionally, such resource limitations render local governments unable to employ specialists, resulting in a lack of manpower.

The inadequacy of the existing legislation of the central government is one of the important problems restricting urban development. Cities seldom focus on how to orient themselves in the international context and how to connect with local grassroots groups and the public in international-level climate negotiations; this approach might be the main point of future development. Given the challenges of horizontal governance, a cooperation mechanism has not yet been developed for cross-sectoral integration, and intercity coalitions have not yet become a systematic structure in Taiwan. Even if cities have successfully established units in charge of energy saving and carbon reduction, coordinating across sectors remains necessary to truly unify and coordinate these units.

From a political perspective, electorally oriented local leaders often influence the priority of climate issues, which is one of the limitations of urban climate action. Disputes regarding various political values, especially the demand for economic development, often result in climate issues coming in at low priority

on the political agenda. Compromises are sometimes necessary because of local economic demands. Consequently, the political will of city leaders becomes pivotal in influencing climate policy. However, in the context of electoral politics, policy formulation has always been tenure oriented. Thus, continuity in long-term city planning for climate issues is difficult to achieve.

To sum up, cities encounter many of the same problems, and many of these problems originate from multilevel governance, as well as interactions and coordination among stakeholders. In early stages, cities encountered the problem of climate change issues lacking a coordination unit. In response, local governments gradually integrated units related to energy saving and carbon reduction into a task force unit in charge. The cross-border scale is high for climate issues, and many projects overlap between different sectors; thus, such institutions should employ a communication platform and decrease the problem of departmental division by increasing these units' orientation toward climate issues. In the foreseeable future, cities will play a more important role in international climate governance. In the crucial context of global post-Kyoto climate negotiation, the structural and systematic transformation that may be effected by the Taiwanese government's urban climate strategies will require further study.

Reference

Tze-Luen Lin. (2016). "The Barriers and Challenges of Urban Climate Governance in Taiwan: A Multilevel Governance Perspective," a book chapter of *Adapting to Climate Change through Local Strategic Planning: Processes, Experiences and Knowledge* edited by Hsiao-Lan Liu and Chia-Tsung Yeh, 121-153. Taipei: Chan's Arch-Publishing Co. Ltd.

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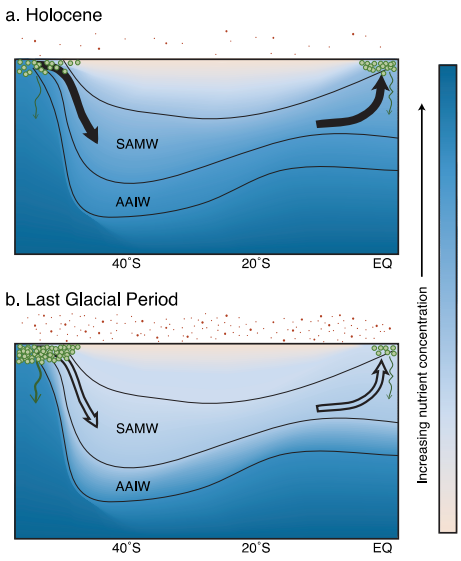
With climate change, fertilizing oceans could be a zero-sum game

Scientists plumbing the depths of the central equatorial Pacific Ocean have found ancient sediments suggesting that one proposed way to mitigate climate warming—fertilizing the oceans with iron to produce more carbon-eating algae—may not necessarily work as envisioned.

Plants need trace amounts of iron to perform photosynthesis, but certain parts of the oceans lack iron, and algae are therefore scarce in those areas. Recent shipboard experiments have shown that when researchers dump iron particles into such areas, it can boost growth. The algae draw the greenhouse gas carbon dioxide from the air to help build their bodies, so fertilization on a large scale could, theoretically, reduce atmospheric CO_2. Seafloor sediments show that during past ice ages, more iron-rich dust blew from chilly, barren landmasses into the oceans, apparently producing more algae in these areas and presumably also producing a natural cooling effect. Some scientists believe that iron fertilization, along with the corresponding drop in CO_2, is one reason why ice ages become icy and remain so.

The equatorial Pacific Ocean is one such high-nutrient, low-chlorophyll region in the global ocean. In such regions, the consumption of the available macro-nutrients such as nitrate and phosphate is thought to be limited in part by the low abundance of the critical micro-nutri-



Schematic understanding of the nutrient dynamics between the Holocene and the Last Glacial Period. Greater glacial productivity in the Subantarctic left a smaller inventory of nutrients to be subducted into the thermocline during Subantarctic Mode Water formation, thereby lowering the supply of nutrients to equatorial upwelling regions. (Figure from Costa et al., 2016)

Lamont-Doherty Earth Observatory's research vessel Marcus G. Langseth sailed to the central equatorial Pacific in May, 2012.

Planktonic foraminifer. (Figure from http://www.jamstec.go.jp/res/ress/kimopy/foraminifera/G_sacculifer/)

ent iron. Greater deposition of atmospheric dust may have fertilized the equatorial Pacific with iron during the last ice age—the Last Glacial Period (LGP)—but the effect of increased ice-age dust fluxes on primary productivity in the equatorial Pacific remains unclear.

To understand the system, Dr. Ren and her collaborators analyzed fossils found in deep sea sediment with the goal of reconstructing past changes in the nitrogen concentration of surface waters and combining the results with side-by-side measurements of dust-borne iron and productivity. They measured the ratios of nitrogen isotopes, which have the same number of protons but differing numbers of neutrons, that were preserved within the carbonate shells of a group of marine microfossils called foraminifera. These measurements in the equatorial Pacific Ocean reveal that although there was more deposition of atmospheric dust during the last ice age than there is today, the productivity of the equatorial Pacific Ocean did not increase; this may have been because the greater nutrient consumption enabled by the iron, mainly in the Southern Ocean, reduced the nutrients available in the equatorial Pacific Ocean and thus also reduced the productivity there.

This new study argues that increased algae growth in one area can inhibit growth elsewhere. This is because ocean waters are always moving, and algae also need other nutrients, such as nitrates and phosphates. Given heavy doses of iron, algae in one region may absorb all those other nutrients; by the time the water circulates elsewhere, it has little more to offer, and adding iron is ineffective.

The paper, "No iron fertilization in the equatorial Pacific Ocean during the last ice age," appears on January 28, 2016, in the leading journal Nature (http://www.nature.com/nature/journal/v529/n7587/full/nature16453.html)

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Kassandra M. Costa, Jerry F. McManus, Robert F. Anderson, Haojia Abby Ren, Daniel M. Sigman, Gisela Winckler, Gisela Winckler, Franco Marcantonio and Ana Christina Ravelo. (2016). No iron fertilization in the equatorial Pacific Ocean during the last ice age. *Nature*, 529, 519-522. DOI:10.1038/nature16453

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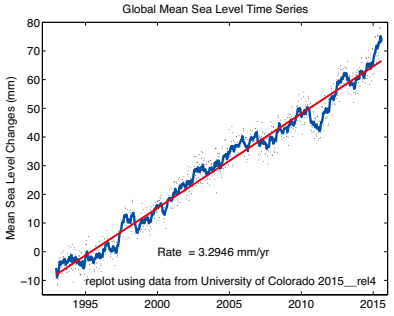
A decade of sea level rise slowed by climate-driven hydrology

Rising sea level is a threat to people living in and near coastal regions. Therefore, accurately predicting and understanding changes in sea level are critical, especially in the face of climate change. However, because of a lack of knowledge regarding the mechanisms that govern the water exchange between the land and the ocean, the fraction of global total water storage on land that contributes to changes in sea level remains unclear.

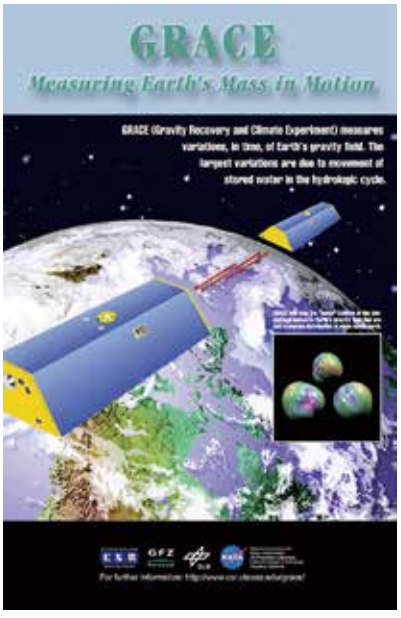
Between 2003 and 2011, mass loss from glaciers and ice sheets continuously increased, whereas the rate of sea level rise decreased to 2.4 mm/year (from approximately 3.3 mm/year between 1993 and 2002). Climate-driven changes in land water storage have been suggested to contribute to this decrease in the rate of sea level rise, but direct observations have not been available to verify this speculation. In a recent study, we found that while the ice sheets and mountain glaciers continue melting, changes in climate between 2003 and 2014 have caused continental land areas such as soils, lakes, and groundwater aquifers to store extra water (approximately 3.2 trillion tons). This storage temporarily decreased the rate of sea level rise by approximately 20% and can be considered a "climate-driven sea level change".

Because of the lack of observations, the effects of climate-driven sea level rise have not been given sufficient attention in Intergovernmental Panel on Climate Change (IPCC) sea level budgets. Recent satellite measurements collected during a time-variable gravity mission, GRACE (Gravity Recovery and Climate Experiment, launched in 2002), have enabled us to estimate the water storage changes at the continental scale and to quantify climate-driven sea level rise. Our results show that from 2003 to 2014, climate-driven land water storage was of opposite sign and similar magnitude as ice losses from glaciers and ice sheets, and was nearly twice as large as mass losses from direct human-driven changes (groundwater withdrawal and dams) in land water storage. Between 2002 and 2014, climate variability resulted in an additional 3200 ± 900 gigatons of water storage on land. This gain partially offset water losses from ice sheets, glaciers, and groundwater pumping and slowed the rate of sea level rise by 0.71 ± 0.20 mm per year. However, such contributions from land water storage are not permanent—they are a form of climate variability and may change in the future. Thus, land-based hydrology has masked the true rate of sea level rise and may also exaggerate the rate of sea level rise in the future.

Our results show that climate-driven changes in land water storage are now observable on a global scale, and these changes are large and necessary for the closure of decadal-scale sea level budgets. The findings



Global mean sea level changes from 1993 to 2015. Data are from Nerem, R. S., D. Chambers, C. Choe, and G. T. Mitchum. "Estimating Mean Sea Level Change from the TOPEX and Jason Altimeter Missions." *Marine Geodesy* 33, no. 1 supp 1 (2010): 435.



Gravity Recovery and Climate Experiment (GRACE) mission. This figure was prepared by The University of Texas Center for Space Research as part of a collaborative effort with the NASA Jet Propulsion Laboratory and the GeoForschungsZentrum Potsdam.

improve upon previous estimates by accounting for feedback between the land, ocean, and atmosphere, and highlight the importance of the land-hydrological cycle and its interactions with climate when assigning contributions to changes in sea level.

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Recent increases in extreme rainfall during typhoons in Taiwan

Role of global warming questionable

Taiwan, which is situated in one of the main paths of western North Pacific tropical cyclones (TCs), has experienced a series of TCs with an extraordinary amount of rainfall since the late 1990s. As of 2015, 11 of the top 15 typhoons based on total rainfall since hourly rainfall observations began in 1960 have occurred in the 21st century. The most extreme case was the record-breaking Typhoon Morakot in 2009. This event caused considerable economic losses and casualties and became the first natural disaster in Taiwan to trigger the resignation of the Premier. Some scientists have warned that because of anthropogenic global warming, this large increasing trend in extreme rainfall will continue into the future with dire consequences,as has been widely reported in the media.

The assertion that global warming will cause a dramatic increase in rainfall in Taiwan is based on the fact that as the temperature rises, the capacity of water vapor in the air expands. The thermodynamic law governing this relationship predicts that for every 1 °C of warming, the water vapor capacity increases by 7%. Therefore, the probability and amount of extreme rainfall will increase, and dynamic storm processes can further increase these effects through feedback mechanisms.

A team of researchers from the National Taiwan University (NTU) Department of Atmospheric Sciences led by Professor Hung-Chi Kuo and including doctoral students Yi-Ting Yang (now a postdoctoral researcher) and Li-Huang Hsu collaborated with Distinguished Professor Chih-Pei Chang (visiting from the U.S. Naval Postgraduate School) to tackle this problem. They found that while the increase in rainfall in recent decades is a manifestation of climate change, it would be a mistake to attribute the apparently large increasing trend of typhoon rainfall to anthropogenic global warming[1,2].

The research team usedhourly rainfall data averaged over 21 stations in Taiwan (Fig. 1a) and collected during the 91 typhoons that made landfall from 1960-2015. When all typhoons are considered together, the rainfall intensity exhibitsa large increasing trend over the period. To look for the possible cause of this trend, they separated the typhoons according to the track type of each storm, as defined by the Central Weather Bureau, and focused on the three leading track types that directly cross Taiwan:the Northern type (N, Fig. 1b), Central type (C, Fig. 1c), and Southern type (S, Fig. 1d). The average separation between adjacent track types is approximately 110 km, which is about half of the length of the Central Mountain Range (CMR) shown in Fig. 1a.

An important factor that affects the amount of typhoon rainfall is the terrain effect of the

CMR, which occurs when the southwesterly flow of the typhoon circulation encounters the western slope of high mountains. This wind-terrain interaction is a major reason why Taiwan typhoons often produce heavy rainfall that causes more damage than that caused by strong winds. Figure 1e shows three examples of low-level typhoon circulation, one for each track type. Here,it is clear that the three track types give rise to different degrees of wind-terrain interactions on the western slope of the CMR. The terrain effect is strongest for the N type and weakest for the S type; hence, the northern track storms should produce more rainfall than the central track storms, which produce more rainfall than the southern track storms. When the research team analyzed the rainfall intensity, they found that this indeed was the case when the typhoon center approaches Taiwan from the east before landing and after the typhoon makes landfall when its center is over land.

However, after the typhoon center exits Taiwan and moves into the Taiwan Strait, the C type storms have approximately the same rainfall intensity as N type storms, both of which are significantly larger than S type storms. This can be explained by another major factor associated with heavy typhoon rainfall. The typhoon season in Taiwan overlaps significantly with the Southwest monsoon season (June – September), during which strong monsoon wind surges often compound the wind-terrain interactions to the southwest of Taiwan and produce enhanced moisture convergence and heavy rainfall, especially after a typhoon exits Taiwan.In this final phase of the life history of a Taiwan typhoon, the wind-monsoon interaction is largest for C type storms (shown in Fig. 1e, where the red arrow indicates the monsoon flow). Notably, this interaction is larger than that associated with N type storms because N type storms are further to the north and away from the South China Sea. Thus, the C type rainfall intensity is more enhanced, resulting in the two types of storms having similar high rainfall intensities. However, although S type centers interact strongly with the Southwest monsoon after exiting land, they have diminished terrain interaction with the CMR; thus, their rainfall intensity over Taiwan is the lowest.

When the three track types are examined separately, the large increasing trend in rainfall intensity in past decades is much less clear. Taiwan has experienced a large increasing trend in typhoon rainfall fortwo reasons. First, N type storms have moved more slowly across Taiwan and therefore produced more rainfall because they remained over land longer on average. Second, more typhoons made landfall in Taiwan during in the 21st century than before, and the bulk of the increased frequency involved C type storms, which, along with the N type storms, produced higher amounts of rainfall than did S type storms. Therefore, the long duration of N type storms and the increased frequency of C type storms have caused the apparent increase in rainfall over Taiwan, In fact, the increasing trend in typhoon intensity is much smaller than that in total typhoon rainfall. This trend was most discernible during the final phase after a typhoon center exited Taiwan.

The next question involves determining why these changes in track type behavior have occurred. Here, it is useful to note that the distance between the different track types is on the order of 110 km, a mesoscale distance, and the largest increase in frequency occurs in C type events, with no bias toward the northern or southern tracks. Therefore, these changes cannot be attributed to the typhoon track changes proposed in some global warming studies, which occur on the order of 1000 km or larger. Moreover, the increase in typhoon frequency is clearly a local phenomenon because over the large western North Pacific basin, the frequency of TCs decreased over the study period. Additionally, the increase in the rainfall intensity during the over-land and exit phases of C type storms and the increase in the duration of N type storms appear both related to the strengthening of the Southwest monsoon in the early 21st century. This strengthening has increased wind-monsoon interactions and therefore rainfall when a storm exits Taiwan. In addition, these changes have slowed the westward movement of typhoons slightly because they oppose the easterly steering flow. The reduction in the steering flow is very small, but the effect becomes significant for N type storms due to the large wind-terrain interaction. This interaction produces large latent heating that is anchored to the terrain, which provides an important stationary forcing mechanism of N type storms and their movements[3].

The final question involves determining whether the strengthening of the southwest monsoon is a result of global warming. The answer is unlikely

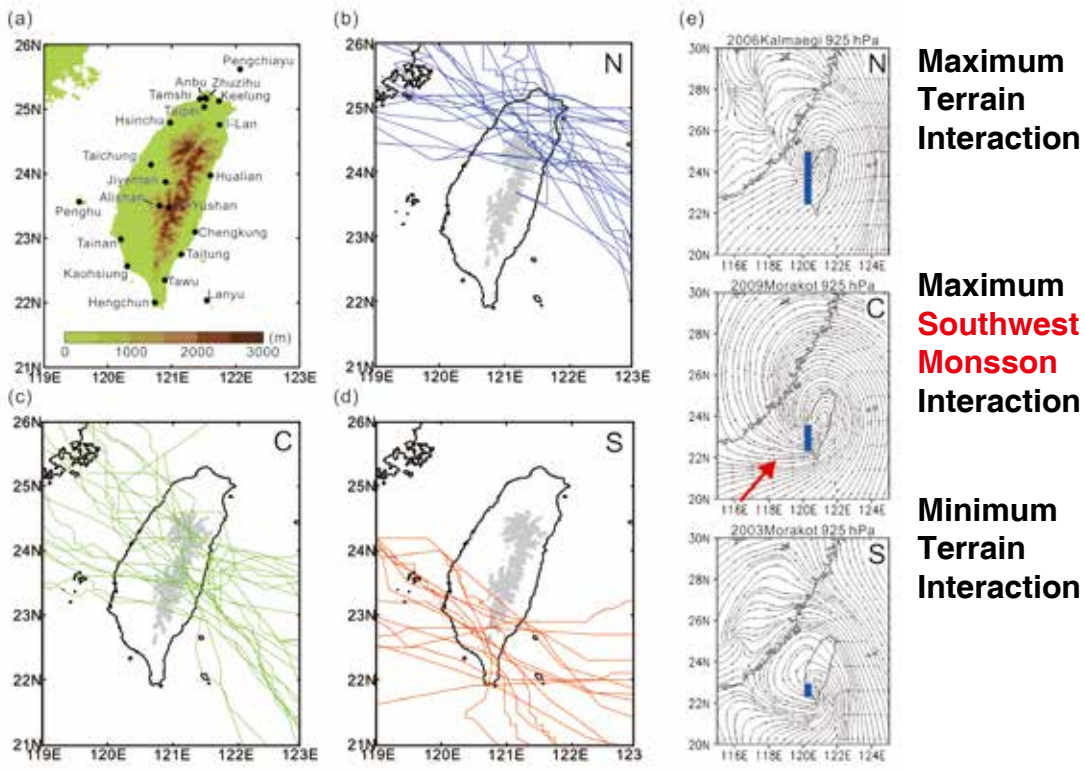

Figure 1. a) Taiwan topography and rainfall stations. b)-d) The northern (N), central (C) and southern type (S) tracks. e) Examples of 925 hPa streamlinesbased on the European Centre for Medium-Range Weather Forecasts - TOGA Global Advanced Analysisof the three track types.

for two important reasons. First, the increasing water vapor capacity with increasing temperature tends to reduce tropical circulation in global warming models, so the Southwest monsoon should be weaker, not stronger. Second, recent analyses[4] comparing the strengthening of the tropical monsoon to decadal-scale oscillations have indicated that the strengthening is better correlated with natural variability, such as Mega ENSO and the Atlantic Multidecadal Oscillation, and is poorly correlated with the north-south hemispheric differences that can serve as an anthropogenic global warming index. The NTU research team concludes that the apparent increasing trend in extreme rainfall in Taiwan caused by typhoon activity is likely the result of natural climate variability and anthropogenic global warming does not appear to play an important role.

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How sure is sure? Are we absolutely certain when and where floods occur?

Providing probabilistic flood forecasts using an ensemble precipitation forecasting technique

Dr. Edward Norton Lorenz, an American mathematician and meteorologist, realized that small differences in the atmosphere or an atmosphere model can lead to unsuspected results. He stated that "When a butterfly flutters its wings in one part of the world, it can eventually cause a hurricane in another." The statement later became a world-renowned concept called the "butterfly effect". Because considerable uncertainty exists in the atmosphere, it is difficult to make accurate weather forecasts. Considering the difficulty of accurate weather forecasting, how can we develop a method of predicting future scenarios? National Taiwan University, National Central University, National Taiwan Normal University, Chinese Culture University, the Central Weather Bureau, the National Center for High-Performance Computing, the Taiwan Typhoon and Flood Research Institute, and the National Science and Technology Center for Disaster Reduction conducted an ensemble precipitation forecasting experiment called the Taiwan cooperative precipitation ensemble forecasting experiment (TAPEX). TAPEX includes various physical model schemes and data assimilation techniques, as well as initial and boundary conditions. Such models provide a wide range of potential future states of the atmosphere. Given quantitative precipitation forecasting information, the flood risk at the township level can be rapidly evaluated based on a rainfall threshold concept. Professor Gwo-Fong Lin led a research team in developing a statistics-based flood forecasting model that provides probabilistic flood forecasts in Taiwan during a typhoon. The model considers different sources of information, such as the designed capacities of storm sewer systems, a flood inundation potential database, and historical flood observations, to identify the cumulative rainfall thresholds that will trigger floods. Using 24-, 48- and 72-h precipitation forecasts from TAPEX, the model can assess the flooding potential with two levels of risk and a 3-day lead time. The model was first applied to Pingtung County and can now be used in analyses of the entire island of Taiwan. A dataset of typhoon storms from 2010 to 2015 was used to evaluate the model performance. Although the model cannot predict the exact location and time of flooding, its probability-based results can help decision makers evaluate the reliability of the forecasts and take appropriate measures. Although the model's performance decreases when the lead time increases due to increased uncertainty, the model has considerable potential as a valuable reference for improving emergency responses and alleviating the loss of lives and property due to flooding.

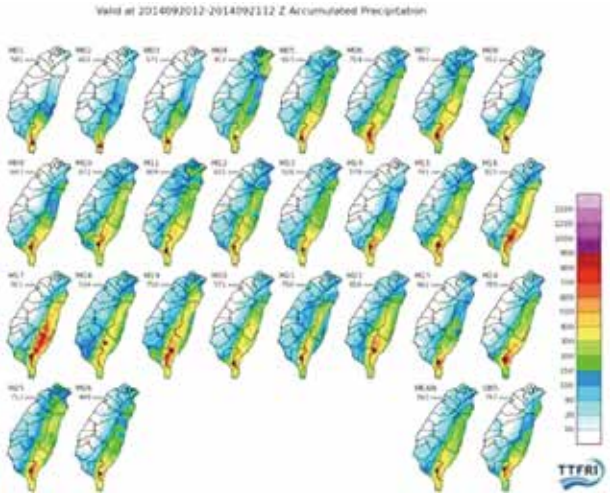

Figure 1. TAPEX rainfall forecasts for a typhoon

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An ancient cold event 12 thousand years ago provides clues for future climate change

Dr. Chuan-Chou Shen, a Distinguished Professor in the Department of Geosciences, National Taiwan University (NTU), collaborated with Dr. Jud Partin of the University of Texas (UT) at Austin to publish new research results regarding a well-known abrupt cooling event 12 thousand years ago (ka), called the Younger Dryas, in the renowned journal Nature Communications on September 2, 2015 (ref. 1). In this study, researchers used stalagmite records to show that this event occurred rapidly, over decades, in North Atlantic regions but gradually, over centuries, in low-latitude Pacific zones. This finding could offer important clues for future global climate change.

The Younger Dryas affected the global climate at 12.8 to 11.6 ka. It was induced by a sudden influx of freshwater into the North Atlantic and the consequent slowdown of ocean currents due to multi-millennial global warming after the end of the last glacial maximum at 18 ka. Greenland ice core records suggest that the onset of this event occurred rapidly, possibly within 3 years at 12.8 ka, and termination lasted for 60 years at 11.6 ka.

The research team combined new stalagmite-inferred rainfall records from Palawan, Philippines, and published records to highlight the difference between regional climate responses to the Younger Dryas. Although the onset and termination are synchronous across the global records, tropical hydroclimate changes were more gradual (> 100 years) than the abrupt (10-100 years) temperature changes in the North Atlantic Ocean during the climate transition.

A recent on-site monitoring study indicated that the ocean currents in the North Atlantic are already slowing down. Contemporary global summer temperatures have reached record highs; combined with extremely cold winters in the northern hemisphere, these observations could suggest another possible global cooling event in the near future. If such an abrupt event occurs, it may not produce the same climate shifts as those observed in the North Atlantic. For this case, southern Taiwan could gradually become dry and cold, and northern Taiwan could experience cold but humid winters associated with a strengthened northeastern monsoon.

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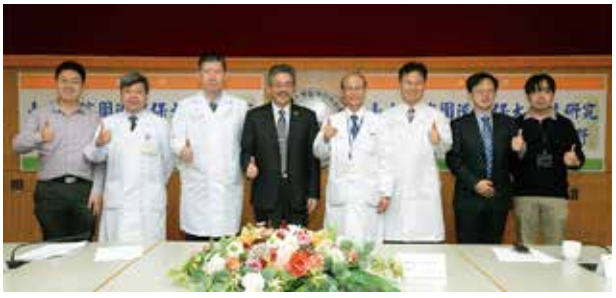
Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone

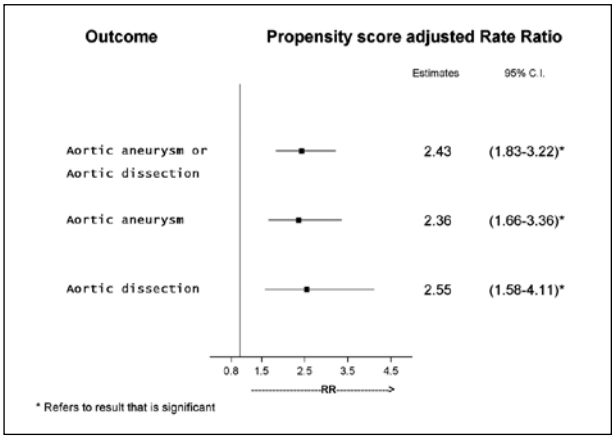
NTU College of Medicine uncovers new global drug safety insights by using big data from the National Health Insurance Database

A research team at the National Taiwan College of Medicine has uncovered new insights into global drug safety. The team discovered a nearly 3-fold increase in the risk of aortic aneurysm and dissection in users of fluoroquinolone, a widely used antibiotic. Fluoroquinolones are widely used for the treatment of bacterial infections in the respiratory tract, intra-abdominal organs, eyes, skin and skin structure, and genitourinary tract. The global prescription of fluoroquinolone antibiotics increased from 4.75 billion pills to 7.81 billion pills between 2000 and 2010. In Taiwan, the number of people taking fluoroquinolones within 1 year increased nearly 1.8 times from 0.5 million to 0.9 million.

With the increasing number of people taking fluoroquinolone antibiotics, once-rare adverse drug events have now become a growing public health problem. Recently, fluoroquinolone has been associated with a series of collagen-related disorders, such as Achilles tendon rupture, tendinopathy in multiple muscle groups, and retinal detachment. As fluoroquinolones may induce the degradation of collagen and cause tendinopathy, this raises the concern of whether fluoroquinolones may cause or aggravate aortic aneurysm and dissection through a similar mechanism. Aortic dissection is defined as a separation of the layers within the aortic wall, while aortic aneurysm is defined as a localized or diffuse dilation of the aorta. Ruptured aortic aneurysms and dissections are associated with high morbidity and mortality rates.

Unfortunately, because aortic aneurysm and dissection are both relatively rare, with only hundreds of new cases per million people, testing the association between fluoroquinolone therapy and aortic aneurysm and dissection by traditional clinical trials is infeasible. Thus, the team decided to use the large Taiwanese National Health Insurance





Research database to test the association between fluoroquinolone therapy and aortic aneurysm and dissection. However, this is not a simple clinical question—it requires input from statisticians and specialists in both infectious diseases and cardiology. Prof. Shan-Chwen Chang and Dr. Chien-Chang Lee assembled a 7-person team to investigate cases of aortic aneurysm or dissection in a Taiwanese population of one million for over 12 years. A total of 1,477 individuals who experienced aortic aneurysm or dissection were identified and matched to 147,700 controls. After propensity score adjustment, the current use of fluoroquinolones was associated with an increased risk of aortic aneurysm or dissection (rate ratio [RR]=2.43, 95% CI, 1.83-3.22). The risk for this serious yet rare adverse

event should be considered in benefit-risk calculations for fluoroquinolone use, and further research must explore how these important antibiotics affect collagen.

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A simple, powerful, and widely applicable 3-microRNA scoring system for prognostication in de novo acute myeloid leukemia patients

Acute myeloid leukemia (AML) is a heterogeneous disease with various pathogenesis, treatment responses and clinical outcomes. Personalized treatment according to individual patient risk could both improve patient survival and reduce treatment side effects.

MicroRNAs are a class of small, non-coding RNAs that are derived from precursor RNAs processed by a protein complex containing Dicer and Drosha. They regulate gene expression post-transcriptionally through either mRNA degradation or translation inhibition. In AML, microRNAs are involved in hematopoietic cell differentiation, proliferation, and survival and can affect treatment responses and outcomes.

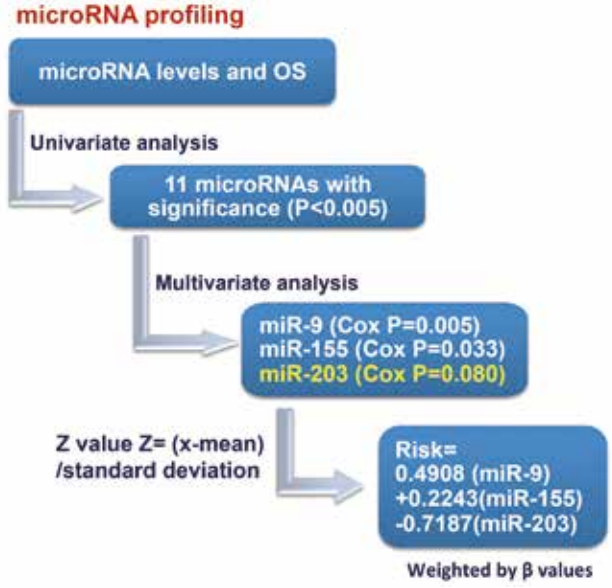

Figure 1. Analysis of miRNA array data, selection of microRNAs whose expressions are associated with survival, and construction of a microRNA scoring system

Using univariate Cox analysis , eleven microRNAs are selected from the microRNA array data whose expressions are significantly associated with overall survival (OS). By multivariate Cox model, expressions of three microRNA are identified as independent prognostic factors. High expression of miR-9 and miR-155 were independently associated with poor OS, while that of miR-203 had a trend of association with favorable OS. By focusing these 3 microRNAs, a risk scoring system is constructed:

Risk = 0.4908 [hsa-miR-9-5p] + 0.2243 [hsa-miR-155-5p] - 0.7187 [hsa-miR-203], where the weights of microRNAs are beta values from multivariate Cox analysis and the expression levels of microRNAs are z-transformed (ie. subtracting the mean and then divided by the standard deviation) across patients so that each microRNA has zero mean and unit standard deviation.

In collaboration with prof. Eric Y. Chuang's team at the Graduate Institute of Biomedical Electronics and Bioinformatics, prof. Hwei-Fang Tien and Wen-Chien Chou and the leukemia research team at the Division of Hematology, Department of Internal Medicine, comprehensively profiled microRNAs in 138 AML patients and found that high expression of hsa-miR-9-5p and hsa-miR-155-5p independently predicted poor prognosis, whereas high hsa-miR-203 tended to indicate a favorable outcome (Figure 1). They constructed a scoring system from the expression of these 3 microRNAs by considering the weight of each. The scores correlated with distinct clinical and biological features and outperformed single microRNA expression in prognostication. The power of this signature was validated by another independent AML cohort from the Cancer Genome Atlas (TCGA). Higher scores were associated with shorter overall survival (Figure 2) independent of other well-known prognostic factors, such as age, white blood cell counts, cytogenetics and molecular mutations. By analyzing mRNA expression profiles, they identified several cancer-related pathways that were highly correlated with the prognostic microRNA signature (Figure 3).

This 3-microRNA scoring system is simple, powerful, and widely applicable for the risk stratification of AML patients. From a practical point of view, these three microRNAs can be analyzed by simple qPCR-based methods for each newly diagnosed AML patient, and the 3-microRNA risk score can be calculated. The procedures are inexpensive and fast and can be performed in a high-throughput manner to help clinicians choose the proper treatment for individual patients.

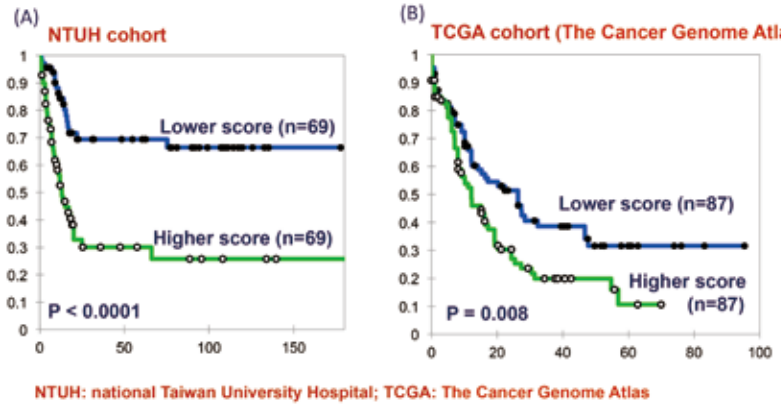

Figure 2. High MicroRNA Score Predicts Poor Overall Survival

The Kaplan Meier curves for overall survival (OS) according to the scores. (A) In NTUH discovery set, patients with lower scores have significant longer OS than those with higher scores (median not reached vs.13.5 months, *P<0.0001*); (B) In TCGA validation cohort, the scoring system still holds true (median 26.4 vs 12.2 months, *P=0.008*).

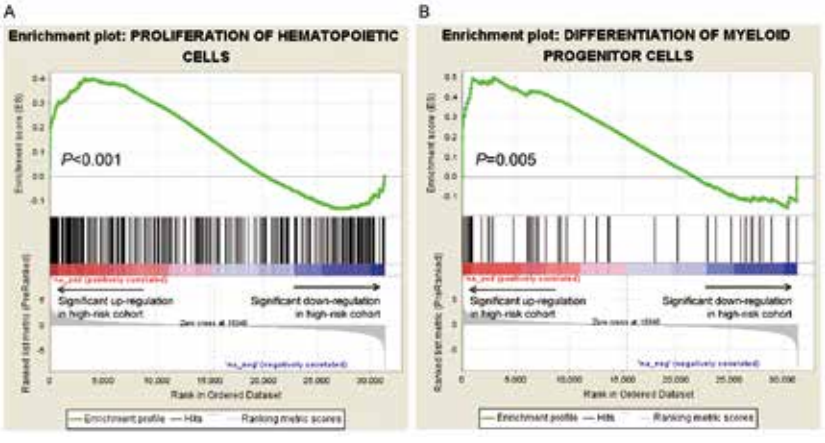

Figure 3. Gene set enrichment analysis (GSEA)

GSEA plots on genes associated with (A) proliferation of hematopoietic cells and (B) differentiation of myeloid progenitor cells. Genes relating to these two functions are highly up-regulated in the patients with high microRNA scores, suggesting significant correlations between these two pathways and the scoring.

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Big data analysis of chinese breast cancer genomics

Exclusive interview with Professor Eric Y. Chuang of YongLin Biomedical Engineering Center

Do you know about the "YongLin Biomedical Engineering Center" at National Taiwan University (NTU)? What is the "Biomedical Engineering Center?" What exactly can it do for us? Why did NTU set this center up? Eric Y. Chuang, the director of the center and also a professor of the Graduate Institute of Biomedical Electronics and Bioinformatics at NTU, is here to give us an introduction to the "YongLin Biomedical Engineering Center."

The "YongLin Biomedical Engineering Center" was set up with help from the donation by the YongLin Foundation under Mr. Terry Gou (Terry Gou, the founder of Foxconn). Mr. Terry Gou's wife died because of breast cancer. The YongLin Healthcare Foundation was named after her and aims to set up a first breast cancer genome database in Taiwan, to promote research on breast cancer. Therefore, the YongLin Foundation and NTU together established the NTU YongLin Biomedical Engineering Center so as to promote the development of the biomedical engineering and medical device industry in Taiwan, to strengthen the exchanges and integration of talent and resources in the industry, and to push the industrialization of R&D achievements forward in the biomedical engineering field at NTU. The scope of work of this particular project includes:

(1) Cooperating with breast cancer oncologists in Taiwan to collect breast cancer specimens with sufficient quantities for exome sequencing.

(2) Establishing a research platform for next-generation sequencing genome database of Chinese breast cancer patients. Breast cancer oncologists may use their personal accounts to review the patients' genetic analysis reports

(3) Establishing a cloud consultation platform website for breast cancer patients, providing

health education and breast cancer information for female breast cancer patients of Chinese descent, and an individualized consulting platform for the breast cancer patients.

Why is it necessary for us to study breast cancer genes? What is the importance of genetic discovery in breast cancer? The earlier news about Angelina Jolie, a famous movie star, who received mastectomy to prevent breast cancer, left a deep impression and sparked a discussion on the importance of breast cancer gene detection. What people don't know is that, up to now, important breast cancer genes that are suitable for gene detection of breast cancer in Chinese patients have not been found. The breast cancer genes BRCA1 and BRCA2 that are clinically applied at present have a relatively very small probability of genetic mutation in Chinese patients, and the mutant gene BRCA1/2 is very rarely seen in most Chinese people. Though such a mutant gene has a very high probability of leading to breast cancer from Caucasian cohorts, the probability of its mutation has been found to be only 10% among breast cancer patients in Taiwan. In other words, there must be other genes causing breast cancer in Chinese patients that have not been found, and therefore, we urgently need a complete breast cancer gene bank for Chinese patients that can be used as a cornerstone for the research of cancer-causing genes in Chinese patients. For this reason, it is quite important to find out the breast cancer prediction genes suitable for Chinese patients with a Chinese breast cancer genome database. The breast cancer genome database for Chinese patients in the Biomedical Engineering Center under the leadership of Director Eric Y. Chuang can meet such a requirement.

The breast cancer genome database can serve as an important reference in gene research for breast cancer oncologists. Breast cancer oncologists can come in contact with many breast cancer patients, yet researchers cannot perform gene analysis for every patient as gene analysis is a huge burden for research. If we have a breast cancer gene bank for Chinese patients, when a doctor finds some interesting cases, he only needs to analyze the genes of these patients, cross-compare them with other cases on the breast cancer gene bank platform, and have exchanges with other researchers or breast cancer patients through the Center's platform. It can accelerate the research and solve relevant problems in the process of researching breast cancer genes, and further discover specific genes causing breast cancer. Therefore, the establishment of the database enables us to find cancer-causing genes important to Chinese patients through relevant research efforts based on the comparison and confirmation of cancer genes, thus bringing forth a completely new milestone for the research of breast cancer genes with Chinese patients.

In order to effectively make this platform achieve its necessary functions, the YongLin Biomedical Engineering Center, in setting up the breast cancer gene bank, has specially used "exome sequencing" experiments for the collection of breast cancer gene data with a large sample quantity. By now, you may have quite a few questions, in particular: Why would a project as simple as setting up a database need the establishment of a huge biomedical engineering center? We can just imagine: if a breast cancer researcher hopes to study the breast cancer gene sequence that he is interested in, in view that there are government regulatory restrictions on research, he needs to first go through administrative procedures to make the protocol in compliance with government regulations before he can lawfully obtain breast cancer tissues from patients. After that, he needs to spend a lot of time and money to obtain the gene sequences. Research laboratories may obtain different rates of correct sequencing due to differences in operator training and equipment. However, the breast cancer database of the YongLin Biomedical Engineering Center can effectively reduce this huge waste of research resources and enable breast cancer research experts to obtain a large quantity of high-precision sequences so that they can concentrate time and efforts on the research of breast cancer genes. Another question is: why should it use

exome sequencing technology? The basic requirement for a database is to be a repository with large amounts of information. We generally believe that the carcinogenic factors of cancer are generated by abnormal protein function due to the mutation of certain important genes. Exons are fragments of nucleotide sequence information of proteins, and sequencing changes in the exons will directly lead to protein mutation. Therefore, the sequencing of this genetic portion will be of greater value. In the human gene bank, exome sequencing accounts for only one percent. That means when the workload of each case can be reduced to one percent, naturally this will greatly reduce the work time and rapidly accumulate case data, thus achieving the purpose of establishing a database with sufficient and large quantities of information in a short period of time.

There are a number of large breast cancer genome databases in other countries now, but a breast cancer genome database for Chinese patients remains lacking. As there are gene differences among different races, compared with other foreign breast cancer genome databases, a breast cancer genome database dedicated to Chinese patients can more effectively eliminate the effects of genetic differences between races so as to precisely ascertain genes causing breast cancer in Chinese patients. Breast cancer patients may, through the consultation platform of the Center, learn about and assess their individual risk of developing breast cancer or the causes for their breast cancer, and also seek effective prevention and therapy guidelines. Finally, in light of the gene characteristics, we can develop testing reagents, therapy guidelines and preventative methods, and even, having ascertained such genes, search among existing drugs or further develop new drugs for treating breast cancer.

"Precision medicine" is the trend in modern medical treatment, and targeted drugs or even more advanced immunotherapy will gradually replace traditional chemotherapy and radiotherapy, which have strong side effects and toxicities. All of this will be based on the research efforts of discovering cancer-causing genes and their mechanisms. Director Eric Y. Chuang of YongLin Biomedical Engineering Center is an excellent scholar, and particularly with a biomedical background, he has made outstanding achievements in integrating biomedical engineering information in a cross-disciplinary manner. The team led by Director Chuang is composed of excellent talent from the College of Electrical Engineering and Computer Science and from National Taiwan University Hospital. Director Chuang emphasizes that the breast cancer genome database is a huge information database and a discovery of possible cancer-causing genes by comparative analysis based on this huge database requires an outstanding information processing capacity. Taiwan has excellent information technology people, and this is an extremely important advantage for Taiwan's biomedical industry. The establishment of the platform of the Biomedical Engineering Center enables Director Chuang and his team to communicate with other researchers and patients on research achievements and questions, so as to join their efforts to realize the potential of curing breast cancer.

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War against HBV

The Interview

Mystery unraveled: Age-dependent immunity against hepatitis B virus

Hepatitis B is a global epidemic. An estimated 240 million people are chronically infected with hepatitis B virus (HBV) worldwide. These chronic carriers have a higher risk of developing cirrhosis and hepatocellular carcinoma, constituting a great burden on the health system, especially in Asian countries.

Prof. Ding-Shinn Chen and Prof. Pei-Jer Chen, renowned HBV experts in Taiwan, have devoted their entire careers to fighting HBV. As hepatitis specialists, they have both conducted several studies aimed at unraveling the mystery surrounding HBV. One of their studies, published in 2015, provides insight into the relationship between the gut microbiota and liver immunity against HBV.

In this interview, the two professors share the results of their study and experience in the war against HBV.

Why do you hypothesize that immunity against HBV is associated with the gut microbiota?

After being infected with HBV, the host may develop acute or chronic hepatitis. Ninety-five percent of adult-acquired infected patients are able to eliminate the virus, leading to spontaneous clearance. However, the immune systems of neonates and children are not mature enough to wipe out the virus. More than 90% of infected neonates and 30% of children aged 1–5 years fail to resolve HBV and develop chronic infections.

This age-dependent immunity is well known, but the underlying mechanism remains poorly understood. The hosts appear to develop immunity against HBV after birth as their immune systems gradually mature.

So, what "teaches" our immunity against HBV?

Unlike other organs, the liver is supplied by both the hepatic artery and the portal vein, accounting for 25% and 75% of the total liver blood flow, respectively. The portal vein collects blood from the gastrointestinal tracts and transports the absorbed substances to the liver. After birth, the neonate starts feeding, and the gut microbiota gradually starts to grow. Because humans also gradually develop liver immunity against HBV after birth, we speculate that the gut microbiota might play a role in liver immunity against HBV.

What is the primary finding of this study?

In this study, adult mice (12 weeks old) could clear HBV after transfection, but their younger counterparts (6 weeks old) remained HBV-positive 26 weeks after transfection. Adult mice lost the ability to clear HBV after elimination of the gut microbiota with antibiotics, which supports our hypothesis that the microbiota plays a crucial role in liver immunity against HBV.

Furthermore, young mice with a loss-of-function Toll-like receptor 4 (TLR4) mutation exhibited rapid HBV clearance, which suggests that the TLR4 pathway may play a role in immune tolerance of HBV.

What was the greatest difficulty in conducting this study?

The main obstacle in proving our hypothesis was building a good experimental model. Generally, mice are the best animal models for studies of human immunological functions. However, because the host range of HBV is very narrow, mice are not susceptible to it. This has been the greatest limitation for HBV studies in the past.

We spent nearly ten years building the hydrodynamic transfection mouse model, which is able to mimic features of HBV infection observed in humans, including age-dependent chronicity. It was not until we developed this system that could we answer our question.

In recent years, many coun-

tries around the globe have used this animal model to conduct HBV studies, especially China, where HBV is an extremely critical public health issue.

What is the next step of this research?

We want to know exactly which molecules released from the gut microbiota stimulate the immune system and which cells in the liver help to build up immunity against HBV. If we can answer these questions, we may be able to find a way to stimulate liver immunity and finally win the war against HBV.

Many HBV carriers are now being treated with antiviral agents such as entecavir. In HBV carriers without cirrhosis, the National Health Insurance only covers the expenditure of these agents during the first three years of treatment. However, some patients develop acute exacerbation or even hepatic failure after discontinuation of these agents. Can we predict the risk of acute exacerbation after drug discontinuation?

Acute exacerbation after drug discontinuation is predictable. The presence of hepatitis B e antigen and a high hepatitis B surface antigen concentration are predictors of relapse. However, the difficulty lies in the timing of discontinuation. If the carrier's liver function improves after a three-year treatment, is it safe to stop the treatment?

There are many criteria for drug discontinuation. Some suggest that treatment should be continued until the hepatitis B surface antigen disappears. However, this is not a practical goal for Asians, who require more time before the hepatitis B surface antigen disappears due to early infection. Others suggest life-long treatment. Nevertheless, HBV is an infectious disease, and we still hope to eliminate the virus one day.

Since the development of direct antiviral agents, curing HCV is no longer a dream. Will a cure for HBV be just around the corner? What are the difficulties in conducting these studies?

The medications for HBV and hepatitis C virus (HCV) are similar, and both are oral agents that inhibit viral replication. The HCV antiviral agent inhibits RNA polymerase and has a high cure rate. In comparison, the antiviral agent for HBV targets reverse transcriptase with a fair control rate. HBV is likely to reemerge in the blood and may induce devastating acute hepatitis once the antiviral agent is discontinued.

What is the main difference between the two viruses?

HCV is an RNA virus. Once it stops replicating, there is no reservoir in our body. In contrast, HBV belongs to the family of DNA viruses. It hides in liver cell nuclei and will integrate into our liver DNA. Our immune system has difficulty eliminating it.

The mechanism by which cells recognize foreign DNA remains poorly understood. If we can better understand how cells recognize foreign DNA, we will be able to develop techniques to help the body clear DNA viruses.

What are the new strategies for treating HBV?

Many new strategies have been proposed, including immune therapy, CRISPR/Cas9 gene editing and viral entry blockade. CRISPR/Cas9, which is now gaining much attention, directly edits the HBV ccc-form DNA in hepatic cells. However, all of these strategies face some difficulties. Some are now undergoing clinical trials, but the initial results have not met expectations.

All of the current anti-HBV agents in clinical use act on reverse transcriptase. In fact, all of these agents were initially developed for the treatment of human immunodeficiency virus (HIV). Most of their anti-HBV properties were serendipitously discovered when treating patients with both HIV and HBV infections.

Many researchers are devoted to developing new anti-HBV agents. However, HBV is a very clever and tricky virus. There are still many challenges ahead!

What are the strategies of the WHO (World Health Organization) for controlling the viral hepatitis epidemic?

The WHO proposed Sustainable Development Goals (SDGs) for viral hepatitis in 2015. The SDGs are composed of three global targets, including reducing new chronic viral hepatitis

infections by 90%, reducing the number of deaths due to viral hepatitis by 65% and providing proper treatment to 80% of eligible persons with chronic hepatitis infections by 2030.

In fact, viral hepatitis has long been neglected by the WHO, which mainly focused on HIV, malaria and tuberculosis. However, the number of deaths caused by viral hepatitis, especially in Asian countries, is higher than that of the above three infectious diseases.

It was wise for the WHO to propose the SGDs for viral hepatitis. Because almost all countries follow the health policies proposed by the WHO, this will make it easier to raise the awareness on a global scale.

What are the other major difficulties in preventing HBV on a global scale?

First, there are still no medications to cure chronic HBV infection. Second, the availability of screening tools is still low in developing countries with limited medical resources. Third, in some countries, especially China, those who are infected with HBV still suffer from social stigma.

On the other hand, although the vertical transmission of HBV can be prevented by hepatitis B immunoglobulins and the HBV vaccine, if the carrier mother has a very high viral load, there is still a 10% chance that her neonates will become carriers even with the above measures.

How can the 10% vertical transmission be prevented?

Prof. MH Chang, a renowned pediatric doctor at National Taiwan University, has conducted many studies on this topic. Based on what was known about the prevention of HIV vertical transmission, anti-HBV agents were administered during the last trimester of pregnancy. The initial study results are quite promising. We hope vertical transmission cases in Taiwan can be eradicated one day.

How did you persuade the government to adopt a universal neonatal HBV vaccination in the 1980s? Did you face any difficulties in promoting the policy to the general population?

HBV was already a serious medical problem in Taiwan in the 1970s. There were no effective medications or vaccines back then, and many people died miserably every year. As a result, when HBV vaccines first came out in the 1980s, many Taiwanese experts tried very hard to persuade the government to implement mass vaccinations. Although it was too late to treat patients who already had HBV, we hoped that vaccinations could save the next generation.

Luckily, in the early 1980s, Taiwan's economy began to boom. The government was convinced and was able to spend more money on infrastructure and health care. They invited experts from different disciplines to discuss policies. With increasing evidence suggesting that HBV was a serious problem, my mentor, Professor Juei-Low Sung, called for neonatal vaccinations in the meetings. Finally, the government started the nationwide neonatal vaccination policy in 1984.

In the early years after implementing neonatal vaccination, the general population and even some physicians did not know the importance of HBV vaccinations. Some doctors even opposed the policy. They criticized the policy makers for exposing Taiwan's neonates to unknown risks for nothing but their own fame. This affected the public opinion and caused much trouble in implementing the policy at that time.

As a result, the government held an international symposium, inviting both international HBV experts and local experts, as well as local doctors, who opposed the policy. After days of discussion, most were persuaded, and the policy was successfully promoted.

The hepatitis C virus (HCV) is another critical public health issue in Taiwan. What are the past, present and future strategies for HCV control in Taiwan?

HCV was first identified in 1989. After its discovery, we immediately conducted epidemiological studies in 1990 and found that HCV was a killer in Taiwan second only to HBV.

HCV is a unique virus. A high percentage of the infected persons will develop chronic in-

fections. Most do not exhibit any symptoms after being infected. Over time, these chronic infected persons may develop cirrhosis and hepatocellular carcinoma 3-4 decades later.

The importance of HCV has been neglected for a long time. However, the prevalence of HCV infection in adults is approximately 2% to 4% in Taiwan. Among infected adults, 70% to 80% (approximately 600,000 people) develop chronic infections.

Prevention of HCV is quite simple and includes the use of disposable needles and syringes, the sterilization of surgical instruments, and the screening of donated blood for the presence of hepatitis viruses. Using these measures, the number of new cases of infection decreased drastically.

However, what can we do for chronic HCV-infected persons?

Two to three decades ago, interferon was the only treatment for HCV and had high relapse rates after discontinuation, and the cure rate was less than 5%. As a result, in early 1990, we at the National Taiwan University Hospital launched studies on HCV treatment and found that combining ribavirin with interferon resulted in a higher cure rate (approximately 50%). Later, by using long-acting interferons, the cure rate of this combination therapy increased to 70-75%.

However, the combination of these two medication was not perfect. The cure rate was still low, approximately 25% to 55%, in white and black populations due to the host genotype. In addition, the side effects of these two drugs limited their usage. Interferon causes hematopoietic suppression, flu-like symptoms, depression and hair loss, and ribavirin causes hemolytic anemia. Many patients could not tolerate these side effects and were thus unable to receive proper treatment.

Therefore, new agents were developed. A 90-95% cure rate was achieved with the so-called direct-acting antivirals (DAAs) within only 3-6 months of treatment. However, the drugs were terribly expensive. Initially, a 3- to 6-month-course of treatment cost approximately 94,000 US dollars. The patients could barely afford the drugs without health insurance, which sparked much criticism.

HCV is still an important health issue in Taiwan. We hope that these new drugs will be covered by the National Health Insurance (NHI) to ensure appropriate treatment for these patients. However, finances are still the key issue. The Taiwanese government has already negotiated with some pharmaceutical companies, and the new anti-HCV DAAs will be covered by the NHI in 2017.

As a result of many people's efforts, the death rates caused by hepatocellular carcinoma and cirrhosis in Taiwan have gradually declined. Doctors and researchers are responsible for providing high-quality study results to convince our government to enact policies.

The hepatitis D virus (HDV) is quite mysterious. How is HDV treated and prevented?

The hepatitis D virus (HDV) is quite special. It requires the envelope of HBV to form its viral particle. If there is no HBV envelope, HDV cannot complete its life cycle and therefore will not survive.

If we can prevent HBV transmission, HDV will no longer be a problem.

However, once infected with HDV, it is difficult to eradicate the virus. Chronic HDV carriers may develop cirrhosis and fulminant hepatitis. At present, there is no effective medication for HDV infection. Prolonged administration of interferon may have an effect, but only a minority of patients are able to clear the virus.

The prevalence of HDV infection in asymptomatic HBV carriers in Taiwan was approximately 4% according to our study 20 years ago. No similar study has been conducted in recent years, but the prevalence today may be lower. However, in intravenous drug users, the prevalence of HDV infection remains high; therefore, we should still pay attention to HDV.

As HDV is easy to prevent and its prevalence in HBV carriers is low, the number of studies of HDV and the development of new drugs targeting HDV worldwide have decreased.

The hepatitis E virus (HEV) is

associated with a high mortality rate among pregnant women. What are the reasons for this?

This deadly phenomenon is only observed during the third trimester of pregnancy. There are some hypotheses, including viral replication in the placenta and hormonal changes during pregnancy, but none of them have been validated. HEV can infect many other animals, including monkeys, deer and hogs. However, high mortality rates during the third trimester have not been observed in experimental studies in monkeys. We still do not known the mechanism responsible for this.

HEV is transmitted through the fecal-oral route. As a result, public and personal hygiene is of great importance. Furthermore, an HEV vaccine has recently been developed in China, with good effectiveness according to the clinical trial data.

In addition, the hepatitis A virus (HAV) is another hepatitis virus transmitted through the fecal-oral route. Less than 3% of the young population in Taipei currently has antibodies against HAV. Although the hepatitis A vaccination is effective, the price of the vaccine decreases the willingness of some people to get vaccinated. However, I still advocate that all health care providers without hepatitis A antibodies should receive the vaccination. Doctors and nurses are at high risk because they are likely to be infected through contact with hepatitis A patients, especially when bathing or changing the diapers of infected children.

Any suggestions for medical students and young doctors?

Dream and don't give up!

As a doctor, your mission is to improve people's health. Try your best to take care of your patients or contribute by taking part in public health policies. You must follow your dreams, keep up your enthusiasm and never give up!

Featured Research

The gut microbiota may play a key role in age-dependent HBV clearance

Hepatitis B virus (HBV) is one of the most common infectious diseases worldwide. According to the World Health Organization, more than 2 billion people are infected with HBV, and 240 million people are chronic carriers. These chronic carriers have a higher risk of developing cirrhosis and hepatocellular carcinoma than the general population, placing a great burden on the health care system.

A unique feature of HBV infection in humans is that viral clearance depends heavily on the age of exposure. Ninety-five percent of adult-acquired infections lead to spontaneous clearance, whereas more than 90% of exposed neonates and 30% of children aged 1–5 years fail to resolve HBV and develop chronic infections. It is postulated that "liver tolerance" and "immune immaturity" to HBV result in high viral persistence in the early stage of life but that the maturation of liver immunity later in life allows for HBV clearance. However, this maturation process has not been clarified.

The liver has a unique blood supply system, with one-fourth of the blood supply coming from the hepatic artery and three-fourths of the blood supply coming from the portal vein, which collects blood from the gastrointestinal tract. As a result, it is plausible to speculate that the signal stimulating liver immunity may come from the gastrointestinal tract.

Who is sending out the messages?

In recent years, growing evidence has revealed that the gut microbiota may play a key role in immune system development. Although the liver is not in direct contact with these commensals, constant exposure to microbe-derived metabolites through the gut-liver axis may shape liver immunity. In neonates, the gut microbiota will gradually develop after oral intake and will become stable 2 to 3 years later, which is compatible with the development of liver immunity against HBV.

In January 2015, Professor

Chen and his team published their study, which was mainly about the relationship between the gut microbiota and liver immunity against HBV, in the Proceedings of the National Academy of Sciences of the United States of America (PNAS).

In this study, mice were transfected with HBV and studied. Adult mice (12 weeks old) cleared HBV within 6 weeks after transfection, while their young counterparts (6 weeks old) remained HBV-positive 26 weeks after transfection. In addition, antibiotic-induced sterilization of the gut microbiota at a young age prevented adult mice from rapidly clearing HBV. Possible molecular mechanisms of clearing HBV were elucidated by using mice with specific gene mutations.

Based on the above results, gut microbiota development may be associated with age-dependent HBV clearance. This relationship may guide new treatments aimed at helping neonates eradicate HBV.

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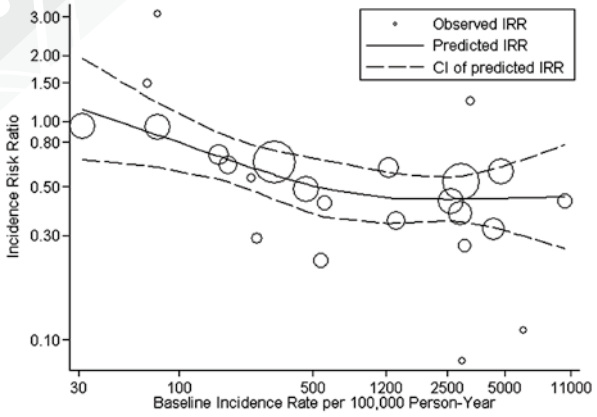
Helicobacter pylori eradication reduces the risk of gastric cancer

Gastric cancer is a major global health threat and is the third-leading cause of cancer deaths worldwide, as the disease causes more than 720,000 deaths per year globally. Gastric cancer detection during a symptomatic stage often results in poor survival and frequent recurrence despite the availability of various modalities that can be used as rescue treatments. As the size of the elderly population is continuously increasing, the International Agency for Research on Cancer has estimated that the current high incidence rate of gastric cancer will remain stable or even increase by 2030 without the development of effective measures for preventing the disease.

Helicobacter pylori is the most important etiologic factor for gastric cancer. It is estimated that 89% of non-cardiac gastric cancers, which account for 78% of gastric cancer cases, are attributable to *H. pylori* infection. Since *H. pylori* can be eradicated with a short-course of antibiotic treatment, identifying and eradicating *H. pylori* infection may represent an effective strategy for reducing the risk of gastric cancer.

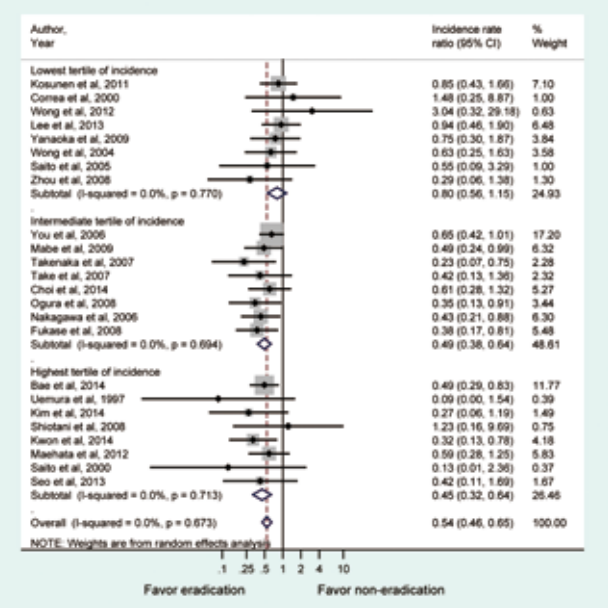
However, in real-life settings, the magnitude of the benefit of *H. pylori* eradication with respect to the risk of subsequent gastric cancer development remains unclear. To address this important question, researchers from the Department of Internal Medicine and the Institute of Epidemiology and Preventive Medicine of National Taiwan University and Baylor College of Medicine in Houston, Texas, USA, have conducted a systematic review and me-



ta-analysis of randomized trials and cohort studies involving both asymptomatic *H. pylori* carriers (i.e., primary prevention) and individuals undergoing endoscopic resection of early gastric cancer (i.e., tertiary prevention) to investigate the association between *H. pylori* eradication and gastric cancer incidence. The study was published in the May 2016 issue of Gastroenterology.

From a total of 8,061 articles, 24 eligible studies (from China, Colombia, Finland, Japan, Korea, and Taiwan) including a total of 48,064 individuals/340,255 person-years and 715 incident gastric cancers were included in the analysis. Gastric cancer developed in 253 of 20,484 infected individuals who received eradication therapy compared with 462 of 27,580 infected individuals who did not receive anti-*H pylori* treatment; thus, eradication therapy yielded a risk reduction of 46% (95% confidence interval: 35% to 54%), and no significant heterogeneity was noted between studies. The benefits of *H. pylori* eradication did not differ according to study design, sex, or follow-up period.

The baseline gastric cancer incidence in each study varied widely from 34.3 to 10,256.4 cases per 100,000 person-years. Researchers also identified a non-linear correlation between baseline gastric cancer incidence and the incidence rate ratio. The upper 95% CI of the incidence rate ratio for eradication decreased to below 1 when the baseline gastric cancer incidence exceeded 150 cases per 100,000 person-years, and the incidence rate ratio continued to decrease concurrently with increasing baseline incidence up to approximately 1,200 cases per 100,000 person-years and then stabilized. These findings indicate that studies on high-risk individuals have superior statistical power and that studies involving low-to-intermediate risk groups have been constrained by insufficient sample sizes



and short follow-up periods.

In conclusion, "*by synthesizing available evidence from multiple populations and clinical scenarios, our study shows that H. pylori eradication reduces gastric cancer risk in all risk groups,*" the authors wrote in an interview with Reuters. The purpose of *H. pylori* eradication is to resolve gastric inflammation, halt gastric mucosal damage progression, prevent further *H. pylori*-induced DNA damage, improve gastric acid secretion, and restore the microbiome to normal. This study provides strong clinical support for the use of a mass eradication program to reduce the enormous disease burden of gastric cancer globally.

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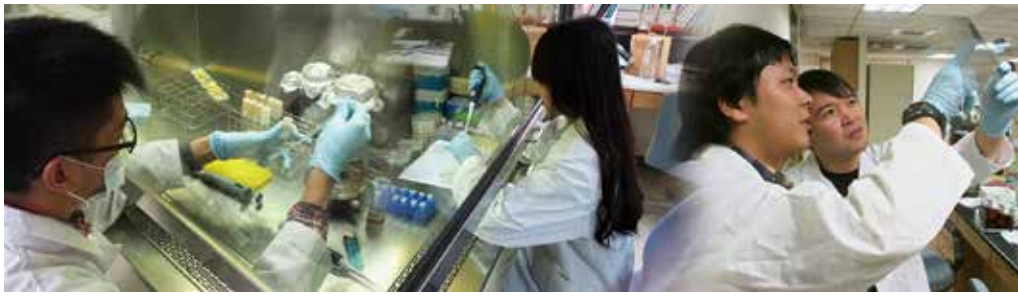
Study reveals inducing endoplasmic reticulum stress regulates golgi apparatus



Researchers led by Prof. Fang-Jen S. Lee of the College of Medicine's Institute of Molecular Medicine recently published an innovative study revealing for the first time that inducing stress in a cell's endoplasmic reticulum (ER) regulates signal transduction and vesicular transport performed by the Golgi apparatus. As numerous investigations have implicated the ER in neurodegenerative and prion diseases, the team's discovery has opened new research directions for understanding the role of endoplasmic reticulum stress in causing these diseases.

The study, titled "Unfolded Protein Response Regulates Yeast Small GTPase Arl1p Activation at Late Golgi via Phosphorylation of Arf GEF Syt1p," attracted the attention of researchers around the world when it appeared in the *Proceedings of the National Academy of Sciences* on March 10.

The endoplasmic reticulum, an organelle in the cells of eukaryotic organisms, serves a crucial role as a starting point for the synthesis, packaging, and transport of proteins and lipids. Proteins manufactured within the endoplasmic reticulum are first folded, processed, and modified before being delivered to the Golgi apparatus. Upon receiving the proteins, the Golgi apparatus makes additional modifications, packages them by type, and ultimately sends them either to the cell membrane via vesicular transport or to the extracellular space through secretion. The proper function of this mechanism is vital for sustaining the life of the organism.

Stress from the cell's external environment or internal changes in its genes will lead to abnormally folded proteins. The accumulation of these abnormal proteins within the endoplasmic reticulum causes endoplasmic reticulum stress as well as an increase in the unfolded protein response.

The endoplasmic reticulum has been reported to affect diseases including Alzheimer's and Parkinson's, as well as diabetes and cancer. Further research into the cellular regulation of the unfolded protein response is expected to significantly advance our understanding of cell physiology and human diseases.

This latest study used the yeast *Saccharomyces cerevisiae* as its model organism. For years, Prof. Lee's laboratory has used this eukaryotic organism, commonly known as brewer's yeast, as a means to understand the regulatory mechanisms controlling vesicular transport.

The study demonstrated that while endoplasmic reticulum stress induced by unfolded proteins influences the distribution of proteins in the Golgi apparatus through Ire1 signal transduction, it also regulates vesicular transport within the Golgi apparatus. Based on these findings, Prof. Lee's team has set a future research goal of gaining a better understanding of the control mechanism through which the Golgi apparatus addresses the accumulation of unfolded proteins and how the Golgi apparatus is impacted by endoplasmic reticulum stress.

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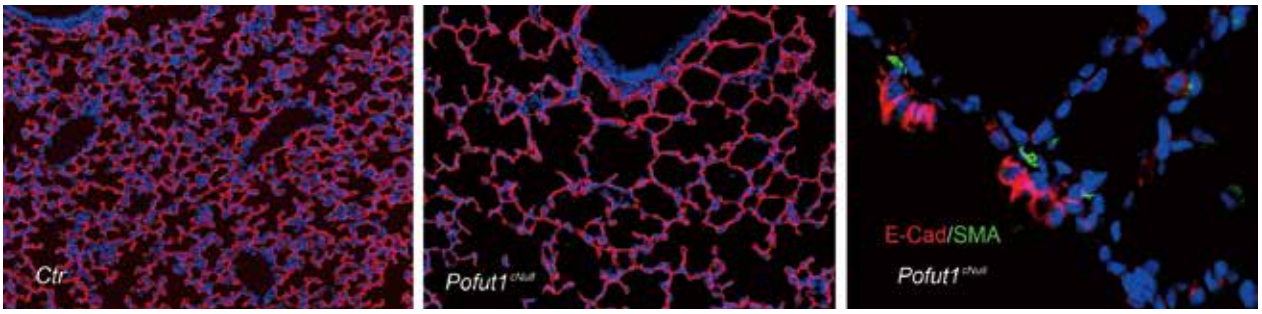
The epithelial-mesenchymal interaction in distal lung development



A research team led by Professor Po-Nien Tsao at the National Taiwan University (NTU) Hospital discovered that Notch signaling is crucial for the differentiation, repair and regeneration of the airway epithelium and could serve as a potential target for the treatment of pulmonary diseases.

How epithelial Notch signaling contributes to alveologenesis is unclear. By using a genetic mouse model, Tsao's team found that *Pofut1F/-:ShhCre/+* mutants (*Pofut1*^{cnull}) exhibited failure to thrive starting at postnatal day 3 with a mortality rate of approximately 80% within 2 weeks after birth. They also observed poor alveolarization in the lungs of the mutant mice. During embryonic development prior to alveolarization, the distal lungs of *Pofut1*^{cnull} mouse appeared similar to those of the control mice. However, at postnatal day 3, the Notch mutant lungs failed to initiate alveolarization, which presented as fewer secondary crests and enlarged air spaces. At postnatal day 21, when alveolarization is mostly complete, the Notch mutant lungs exhibited an emphysema-like phenotype. Furthermore, Tsao's team found that Notch2 but not Notch1 mutant lungs also presented the emphysema-like phenotype. A pulmonary function test confirmed that the Notch2 mutant lungs had dramatically increased static compliance and decreased tissue elasticity. This phenotype mimics that of human chronic obstructive pulmonary disease (COPD) in adults and bronchopulmonary dysplasia (BPD) in preterm infants. The phenotype was caused, at least in part, by poor alveolar myofibroblast differentiation, which resulted from decreased epithelial PDGF-A expression in the Notch mutant lungs. In addition to the alveolar phenotype, Tsao's team also observed a significant decrease in the number of epithelial cells in the distal airway of Notch mutants. Interestingly, this also influenced the development of the surrounding airway smooth muscle, which likely resulted from decreased Wnt7b secretion from the epithelium.

In conclusion, deletion of Notch from the epithelium disrupted alveolar myofibroblast development, which resulted in poor alveologenesis. Moreover, epithelial Notch signaling integrates postnatal morphogenesis of the distal lungs via epithelial-mesenchymal interactions. These data suggest the potential benefit of targeting the Notch pathway in pulmonary disorders that affect the airway or alveolar epithelium.

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How does stress initiate drug relapse?

Drug relapse can be initiated by environmental cues and stress even after extended periods of abstinence, leading to the failure of drug rehabilitation programs. Currently, there are few effective treatments to prevent drug relapse. Therefore, drug relapse is not only an unmet medical need but also an important socioeconomic concern, especially stress-induced drug relapse. The mechanisms by which stress initiates drug relapse remain unclear. The study group led by Prof. Lih-Chu Chiou at the Department of Pharmacology at the Medical College of National Taiwan University revealed a novel mechanism for stress-induced cocaine relapse. This may shed light on the prevention of stress-related drug relapse.

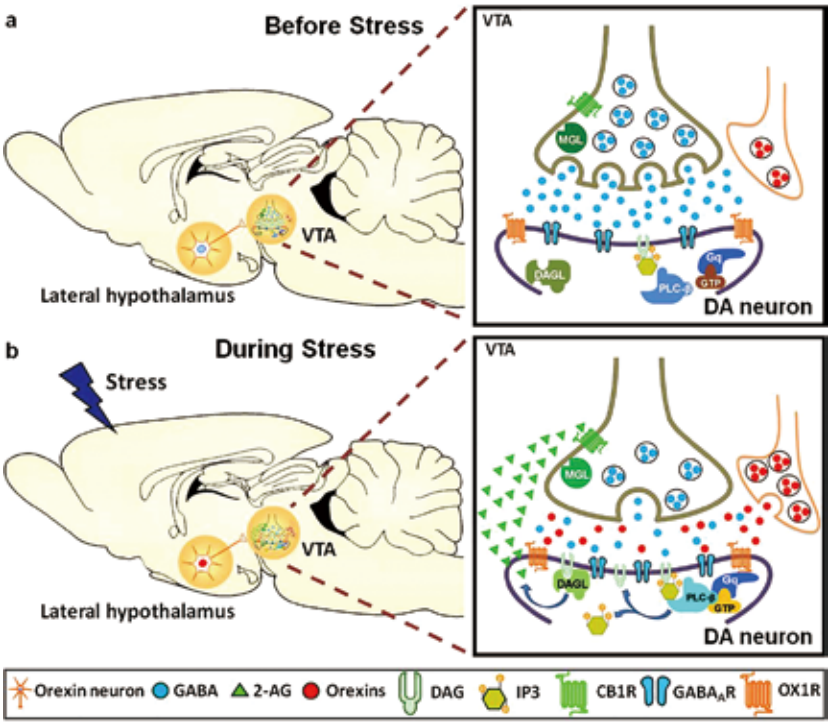

Figure 1. How does stress induce an endocannabinoid-mediated disinhibition in the ventral tagmental area, leading to cocaine relapse?

This scheme describes the neuronal processing that occurs in the lateral hypothalamus (LH) and ventral tagmental area (VTA) circuits (a) before stress and (b) during stress. The boxes on the right are enlarged portions of the synaptic events that occur in a GABAergic synapse onto a dopaminergic neuron in the VTA. During stress, LH orexin neurons are activated and release orexins. The released orexins then activate postsynaptic OX1 receptors on dopaminergic neurons in the VTA. Activation of the OX1 receptor, a Gq-protein coupled receptor, leads to PLC activation, generating DAG that is converted into 2-AG, an endocannabinoid, by DAGL. 2-AG travels retrogradely across the synapse to inhibit GABA release by activating presynaptic CB1 receptors on the GABAergic terminal. Inhibition of GABAergic synaptic neurotransmission onto dopaminergic neurons in the VTA results in activation of the mesolimbic dopaminergic circuitry, leading to a reinstatement of extinguished cocaine CPP, modeling cocaine relapse in humans. Finally, 2-AG is degraded by MAGL, which is located in GABAergic terminals. Thus, the MAGL inhibitor potentiates and prolongs orexin A-induced IPSC depression.

This work was mainly performed by Dr. Li-Wi Tung during his PhD study period at the Graduate Institute of Pharmacology at NTU. The research group found that stress can reinstate extinguished cocaine preference in mice in a conditioned place preference (CPP) training task. The CPP score in this animal model is usually used to evaluate the degree of drug craving. Their results suggest that this stress-reinstated cocaine relapse is mediated by a sequential cascade involving orexins and endocannabinoids.

Orexins consist of a pair of neuropeptides, orexin A and B (also named hypocretin 1 and 2). They are generated by a group of neurons in the hypothalamus, especially in the perifornical area (PeF) and lateral hypothalamus (LH). Their receptors, OX1R and OX2R, are widely distributed throughout the brain, including the ventral tegmental area (VTA), an important brain region for reward processing where dopamine neuron plasticity can be altered by addictive substances. Orexins have been known to play a role in drug seeking behavior in animals. However, the mechanisms by which orexins regulate the VTA dopaminergic activity to provoke drug craving, especially under stressful conditions, remain unclear. Previously, Prof. Chiou's group found that orexins can be released under stress from the

LH to activate a pain-regulating region, the periaqueductal gray (PAG), leading to analgesia. This stress-induced analgesic effect is mediated by a signaling cascade in the PAG, i.e., orexins activate postsynaptic OX1Rs, a family of Gq-protein coupled receptors, resulting in the synthesis of 2-arachydonoylglycerol (2-AG) via the phospholipase C (PLC)-diacylglycerol lipase (DAGL) enzymatic pathway. 2-AG is an endogenous cannabinoid that can produce retrograde inhibition of GABA release (disinhibition) by activating presynaptic cannabinoid 1 receptors (CB1Rs)[1,2].

Inspired by the previous finding in the PAG, Tung et al.[3] validated a hypothesis that this OX1R-PLC-DAGL-2-AG retrograde disinhibition signaling also exists in VTA dopamine neurons and can contribute to stress-induced extinguished cocaine seeking behavior in mice using both electrophysiological and behavioral approaches. Indeed, they found that orexin A inhibited GABAergic transmission via a presynaptic mechanism in dopamine neurons of VTA slices. This effect of orexin A was prevented by the antagonist of OX1Rs or CB1Rs, and by internal inhibition of G protein. It was also prevented by inhibiting the enzymes involved in 2-AG synthesis, PLC and DAGL, and potentiated by inhibiting 2-AG degradation. Furthermore, they found that acute restraint stress activated orexin neurons in the LH, increased both orexin A and 2-AG levels in the VTA, and reinstated extinguished cocaine CPP in mice. This stress-reinstated cocaine CPP was prevented by intra-VTA injection of the antagonist of OX1Rs, CB1Rs or DAGL and was abolished in CB1R-knockout mice. These results suggest a novel mechanism for stress-induced cocaine relapse: acute restraint stress activates LH orexin neurons, releasing orexins to activate postsynaptic OX1Rs on VTA dopaminergic neurons and, through a Gq-protein-PLC-DAGL cascade, generating 2-AG that retrogradely inhibits GABA release through presynaptic CB1Rs, leading to VTA dopaminergic disinhibition and reinstating cocaine CPP.

This finding provides a prospective in the development of OX1R antagonists as a novel therapeutic approach in the prevention of stress-induced cocaine relapse.

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New molecular diagnostic method to identify Hypervirulent *Klebsiella pneumoniae* O1 strains

Klebsiella pneumoniae is an encapsulated gram-negative bacillus that frequently causes outbreaks of nosocomial infections in hospitalized patients. *K. pneumoniae* can also afflict ambulatory persons and cause community-acquired invasive diseases—including pyogenic liver abscess, endophthalmitis, meningitis, empyema, lung abscess, and necrotizing fasciitis. *The* worldwide emergence of multidrug-resistant strains and hypervirulent strains of *K. pneumoniae* has become an increasing clinical challenge and public health concern. A new molecular diagnostic method based on detection of the genetic determinants of lipopolysaccharide (LPS) O-antigen has been developed by Dr. Chi-Tai Fang of National Taiwan University to rapidly and accurately identify hypervirulent *K. pneumonia*e O1 strains. This study was published in March 2016 in the *Journal of Clinical Microbiology*, a distinguished journal of the American Society for Microbiology.

The research was conducted by Dr. Chi-Tai Fang, Professor of Epidemiology and Preventive Medicine at the College of Public Health, National Taiwan University, and his two Master's students, Ms. Yun-Jui Shih and Ms. Cheng-Man Cheong.

K. pneumoniae strains can be distinguished by their capsular polysaccharide (CPS) K-antigen types (77 serotypes) and LPS O-antigen types (9 serotypes). Strains with K1 CPS are extremely virulent, causing metastatic endophthalmitis and meningitis from pyogenic liver abscess. Nevertheless, only 60% of strains causing pyogenic liver abscess are K1 strains. The remaining strains are of K2, K5, K20, K54, K57, and other K types. On the other hand, more than 90% of strains causing pyogenic liver abscess have O1 LPSs. Therefore, O1 is a better marker for virulent *K. pneumoniae* strains capable of causing pyogenic liver abscess. However, previous research has not produced a simple and reliable method for detecting O1 in clinical and epidemiological samples because *K. pneumoniae* O-serotyping is cumbersome and the reagents are not commercially available.

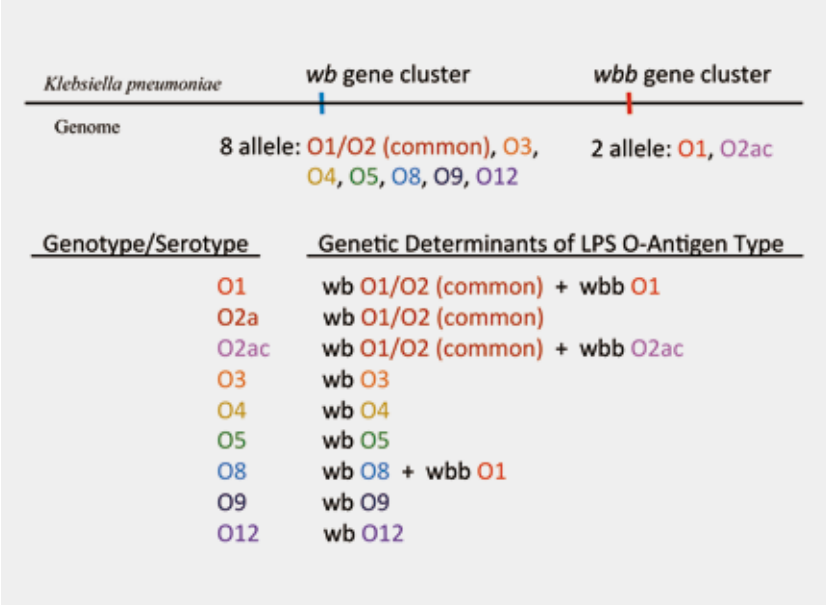

Figure 1. The two genetic determinants of lipopolysaccharide (LPS) O-antigen types in Klebsiella pneumoniae.

To develop a new molecular diagnostic method to quickly and accurately identify O1 *K. pneumoniae*, Dr. Fang and his students sequenced the genetic determinants of LPS O-antigen from O1, O2a, O2ac, O3, O4, O5, O8, O9, and O12 (Figure 1). They then successfully developed allele-specific PCR primers that detect the genes specific to O1 and other O types. His team further tested the sensitivity and specificity of the new molecular detection method against the O and K reference strains provided by the World Health Organization Collaborative Center for *Escher-*

ichia coli and *Klebsiella* at Statens Serum Institut (Copenhagen, Denmark). Both the sensitivity and specificity were found to be 100%.

Given the high accuracy and great convenience, the new PCR detection method represents an important breakthrough in the molecular diagnosis of hypervirulent *K. pneumoniae*. This new technology provides a highly useful tool for clinical and epidemiological investigations of *K. pneumoniae* and associated diseases.

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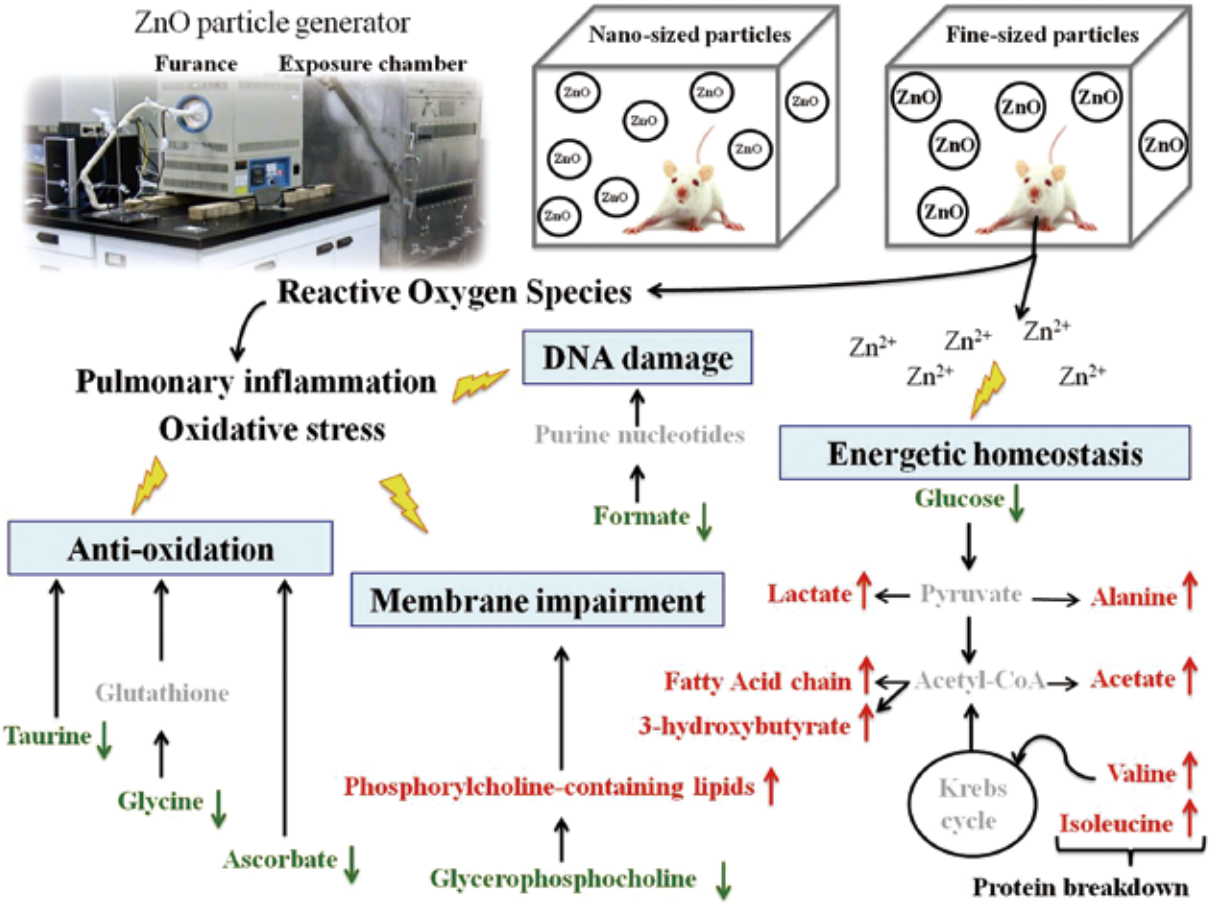
Determining the global metabolic effects of acute inhalation of nano- and fine-sized ZnO particles in the rat lung using an NMR-based metabolomic approach

Nano- and fine-sized zinc oxide (ZnO) particles are widely used for environmental and industrial applications. Previous studies revealed that inhalation of ZnO particles can induce acute occupational inhalation illnesses such as metal fume fever in humans and rats. Although studies have illustrated the association between ZnO-induced adverse effects and pulmonary inflammation, injury, and oxidative stress, the molecular mechanisms in the respiratory system are still unclear. In addition, there is debate regarding the influence of particle size on the toxicity of ZnO particles. Thus, a high-throughput approach was applied to examine the metabolic effects induced by ZnO particles.

This study was published in *Nanotoxicology* in 2016 (10(7): 924–934) and was conducted by Dr. Tsun-Jen Cheng, a professor at the Institute of Occupational Medicine and Industrial Hygiene in the College of Public Health at NTU, Dr. Ching-Yu Lin, an associate professor at the Institute of Environmental Health in the College of Public Health at NTU, and Mr. Sheng-Han Lee, a Ph. D. candidate at the Institute of Environmental Health in the College of Public Health at NTU.

A metabolomic (metabonomic) approach can record a “snapshot” of low-molecular weight metabolites to suggest plausible molecular mechanisms and develop potential biomarkers for different environmental stresses and diseases. To examine the global metabolic responses of the respiratory system of rats that inhaled ZnO particles, a nuclear magnetic resonance (NMR)-based metabolomic approach was used in rats dosed with a series of nano-sized (35 nm) or fine-sized (250 nm) ZnO particles. Bronchoalveolar lavage fluid (BALF) and lung tissues were collected for NMR instrumental analysis and subsequent multivariate statistical analyses such as principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA).

The results of the PCA and



PLSDA models revealed that the metabolome of the BALF and lung tissues exhibited dose-dependent trends after ZnO particle exposure, especially in the samples from the 250 nm ZnO particle exposure group. In addition, metabolites such as isoleucine, valine, acetate, taurine, glycine, formate, ascorbate, glycerophosphocholine, glucose, phosphorylcholine-containing lipids, fatty acyl chains, and trimethylamine n-oxide were perturbed in the respiratory system, especially in rats exposed to fine-sized ZnO particles. These metabolites are associated with membrane stability, cell anti-oxidation, energy metabolism, and DNA damage. The results suggested plausible molecular mechanisms involved in ZnO particle-induced toxicity. In addition, these results confirmed that the mass is critical regarding the particle size-dependent toxicity of ZnO particles. Because ZnO particle exposure is more concentrated at industrial workplaces, metabolomic approaches can provide more comprehensive knowledge of the *in situ* molecular changes and plausible mechanisms of ZnO particle exposure to assess individual risk. Dr. Lin stated, "Future studies to verify the mechanisms of ZnO-induced toxicity and develop biomarkers will further the knowledge for ZnO risk assessment."

Reference

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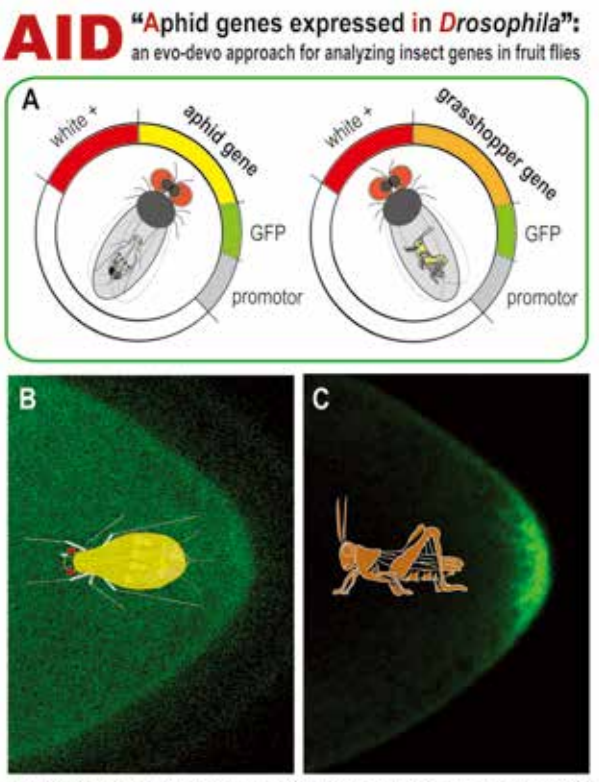
"AID" never fails

Ectopic expression of aphid genes in fruit flies has led to the discovery of sequences critical to the localization of germline protein Vasa to the germ plasm.

Germ plasm, the cytoplasm of germ cells, is enriched with germline determinants for the development of germ cells. If germ plasm is maternally supplied, it is usually assembled in a subcellular region within the oocyte and then inherited by the newly laid eggs. Soon after cellularization, embryonic cells that incorporate germ plasm will become the primordial germ cells. By contrast, if formation of the germ plasm occurs zygotically after fertilization, synthesis of the germline determinants within a small population of cells is initiated by inductive signals released from neighboring somatic cells. Existing records show that most animals do not possess a maternal germ plasm, and a recent study shows that both mice and crickets use bone morphogenetic protein (BMP) signaling to induce germline specification. This suggests that among animal phyla signal induction is a more prevalent and ancestral mode for germline specification.

Before the identification of a maternal germ plasm in the pea aphid *Acyrthosiphon pisum*, a hemipteran insect belonging to the Hemimetabola, the germplasm-driven mode was regarded as a trait only seen in highly derived insects belonging to the Holometabola. For example, during mid-oogenesis in the fruit fly *Drosophila melanogaster, oskar (osk)* mRNA and Osk protein are restricted to the posterior pole of the oocyte, acting as "molecular anchors" to restrict the circulation of other germline determinants to the posterior region. Nonetheless, homologous sequences of *osk* cannot be identified in the genome of *A. pisum*, suggesting that it uses non-osk molecules to attract other germline determinants to form the germ plasm. Regardless of the presence or absence of *osk* in flies and aphids, the conserved germline marker Vasa (Vas) is specifically localized to the maternal germ plasm of both insects.

To understand whether aphid Vas (ApVas1), like *Drosophila* Vas (DmVas), preserves sequence for being localized by Osk, Professor Chun-che Chang—a developmental geneticist in the Department of Entomology at the National Taiwan University (NTU)—proposed to express ApVas1 in *Drosophila* oocytes. This idea, abbreviated as "AID (aphid genes expressed in *Drosophila*), was soon approved by Dr. Ming-der Lin, an alumnus of NTU and a junior faculty member working on *Drosophil*a oogenesis affiliated with the Department of Molecular Biology and Human Genetics at the Tzu Chi University. The Chang and Lin laboratories collaborated to generate transgenic flies containing the *Apvas1* sequence, aiming to analyze whether ApVas1 could be localized to the germ plasm in the posterior region of the developing oocytes.



The AID Project. (A) Making constructs for expressing Vas orthologues of aphids (ApVas1) and grasshoppers (SgV) in the fruit fly *Drosophila melanogaster*; **(B)** ApVas1 protein was evenly distributed in the oocyte; **(C)** SgV was localized to the oocyte posterior. GFP, green fluorescent protein. (Figure and figure legend: C-c. Chang; Photos: S.C. Wang, G.W. Lin, and M.D. Lin)

Not totally unexpectedly, the expression of ApVas1 was initially detected throughout the *Drosophila* oocytes, indicating that ApVas1 lacks sequences to interact with Osk. Given that both ApVas1 and DmVas are RNA helicases containing conserved DEXDc and HELICc domains, systematic "domain

swapping" experiments were then carried out to pinpoint sequences in DmVas that could direct ApVas1 and DmVas itself to the posterior germplasm. The thorough survey led to a remarkable finding: the HELICc domain of DmVas, either when linked to ApVas1 or alone, was essential for posterior localization; moreover, glutamine (Gln) 527 in the HELICc domain of DmVas was found to be critical for the interaction between Vas and Osk. A residue corresponding to Gln527, which is present in the HELICc domains of grasshopper Vas protein but not in those of aphids, crickets, and mice, may explain why only grasshopper Vas could be restricted to the posterior germ plasm. Published results show that segregation of germ cells in the grasshopper *Schistocerca gregaria* is initiated during mid-embryogenesis via signal induction rather than being driven by a maternal germ plasm, indicating that the conserved Gln527 residue has existed in some insect Vas proteins long before the existence of Osk in *Drosophila*. The results mentioned above have been published in *Scientific Reports*, an open-access online journal from the publishers of Nature, in September 2015.

From the evolutionary and developmental study of insect Vas proteins to the discovery of sequences indispensable to the interaction with Osk, members of both the Chang and Lin laboratories felt excited by the unpredicted yet fruitful outcome. Their findings shed light on the evolution of germline specification in insects and on Osk/Vas-dependent germ-plasm assembly in *Drosophila*. They expect that the AID project will evolve to facilitate the functional exploration of additional germline and developmental genes in rising insect models with the "aid" of the powerful approaches used in *Drosophila* genetics.

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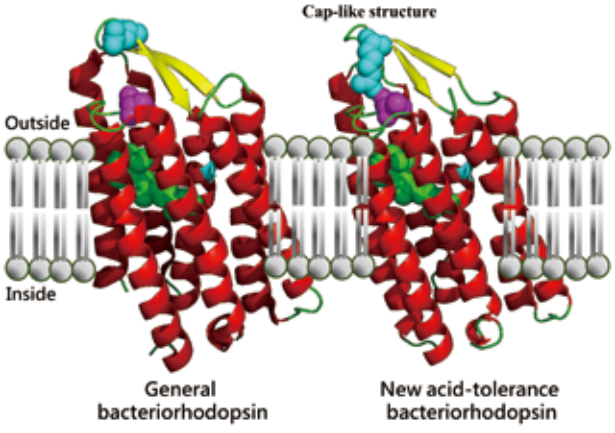
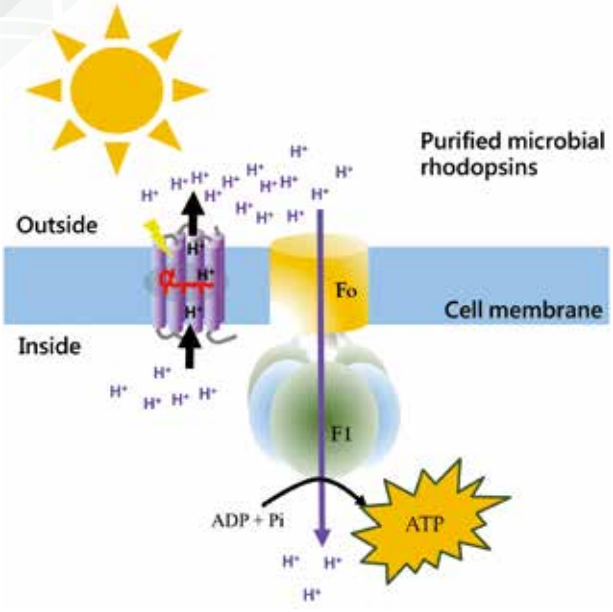
New type of powerful photoreceptor provides new possibilities for applications

For approximately 3.5 billion years, solar light has been the main energy source for all life forms on Earth. Therefore, the ability of proteins to capture solar rays and convert them into usable forms of energy is a "natural" development of all living systems.

The Dead Sea is one of the most saline lakes on Earth, and few microorganisms are found in its waters. Among these microorganisms, the haloarchaeon (a salt-loving archaea) *Haloarcula marismortui* survives such harsh conditions by adopting a unique six-rhodopsin system (1). Thee six rho-





dopsins, often called microbial rhodopsins, are activated by different wavelengths of sun rays and function in light energy harvest and phototaxis.

More than 1000 microbial rhodopsins have been identified in bacteria, eukaryotes and archaea. The rhodopsin involved in capturing light for biological usage is called bacteriorhodopsin.

Bacteriorhodopsin is a light-driven outward proton pump. Upon light activation, it pumps a proton pre-bound in the interior of the protein and re-uptakes another from inside the cell. This process can be carried out repeatedly every ~10 msec. The protons accumulated outside will then re-enter the cell through another protein called F1Fo ATP synthase. Every three protons that reenter will trigger the generation of one ATP, a universal, biologically consumable form of energy. Ultimately, haloarchaea can harvest energy via exposure to sun rays.

A study conducted in the lab of professor Chii-Shen Yang at the College of Life Science unveiled a new kind of bacteriorhodopsin (2) that is at least ten times more powerful than any currently known bacteriorhodopsin in pumping protons outside of the cell. Yang's lab further worked with a research group in Academia Sinica and resolved the atomic structure of this new bacteriorhodopsin. These researchers found a cap-like structure that faced the outside of the cell and was stabilized by some extra chemical bonding networks, leading to functional enhancement.

This research will be noted as an important milestone for the application of such microbial rhodopsins because it provides a lucid principle for future protein engineering to improve the functionality of such proteins.

In this study, Yang's lab used this powerful bacteriorhodopsin to develop an ITO-based device (3) and showed that measurable electric current could be produced upon light activation. This device provides new design possibilities for the development of medical and electronic applications of bacteriorhodopsins.

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Discovery of new species of soldier beetles in Taiwan

NTU entomologists collaborate with Japanese natural history museum on the taxonomy of Cantharidae (soldier beetles)

Comprehensive taxonomic studies are fundamental to biology. They provide accurate identification of materials, which is directly related to the conclusions that can be drawn from results. According to the online database of the Taiwan Catalogue of Life, there are over 20,000 species of insects recorded in Taiwan. Among this large group, the members of Coleoptera, also known as beetles, are the most speciose group and comprise the largest proportion of newly described animals each year.

Beetles belonging to the family Cantharidae, also known as soldier beetles, are small to middle-sized terrestrial beetles occurring on all the habitable continents, with over 5,000 named species and more new taxa waiting for description. Cantharids are characterized by elongated, soft and colorful bodies, are often found in forests and are usually observed visiting flowers. Cantharids are opportunistic predators of invertebrates and also feed on nectar or pollen.

In January 2016, in collaboration with the Japanese entomologist Dr. Yûichi Okushima from the Kurashiki Museum of Natural History, Professor Chiun-Cheng Ko and colleagues from the Department of Entomology published a study in the European Journal of Taxonomy. Prof. Ko

Lycocerus yitingi

Lycocerus evangelium

Lycocerus kintaroi

Lycocerus aurantiacus

supervised his undergraduate intern Yun Hsiao, working on his MOST College Student Research Project on the taxonomy of the *Lycocerus hanatanii* species group (Coleoptera, Cantharidae) from Taiwan.

The team examined over 500 specimens from museum collections in Taiwan, Japan, UK, USA, France, Switzerland and Germany. They discovered four species new to science. One of the new species, *Lycocerus evangelium*, was named for the auspicious circumstances surrounding its discovery: evangelium means "good news" in Latin. The other three new soldier beetles are *L. yitingi, L. kintaroi,* and *L. aurantiacus. L. yitingi* and *L. kintaroi* are named after their collectors, Mr. Yi-Ting Chung and the late Dr. Kintaro Baba, respectively, and *L. aurantiacus* is named for its orange-fringed pronotum.

Global biodiversity currently faces a variety of difficulties, and many species become extinct before they are described. The discovery of new species reminds us that there are still many unknown creatures in Taiwan waiting for discovery and that we should protect our precious homeland and environment.

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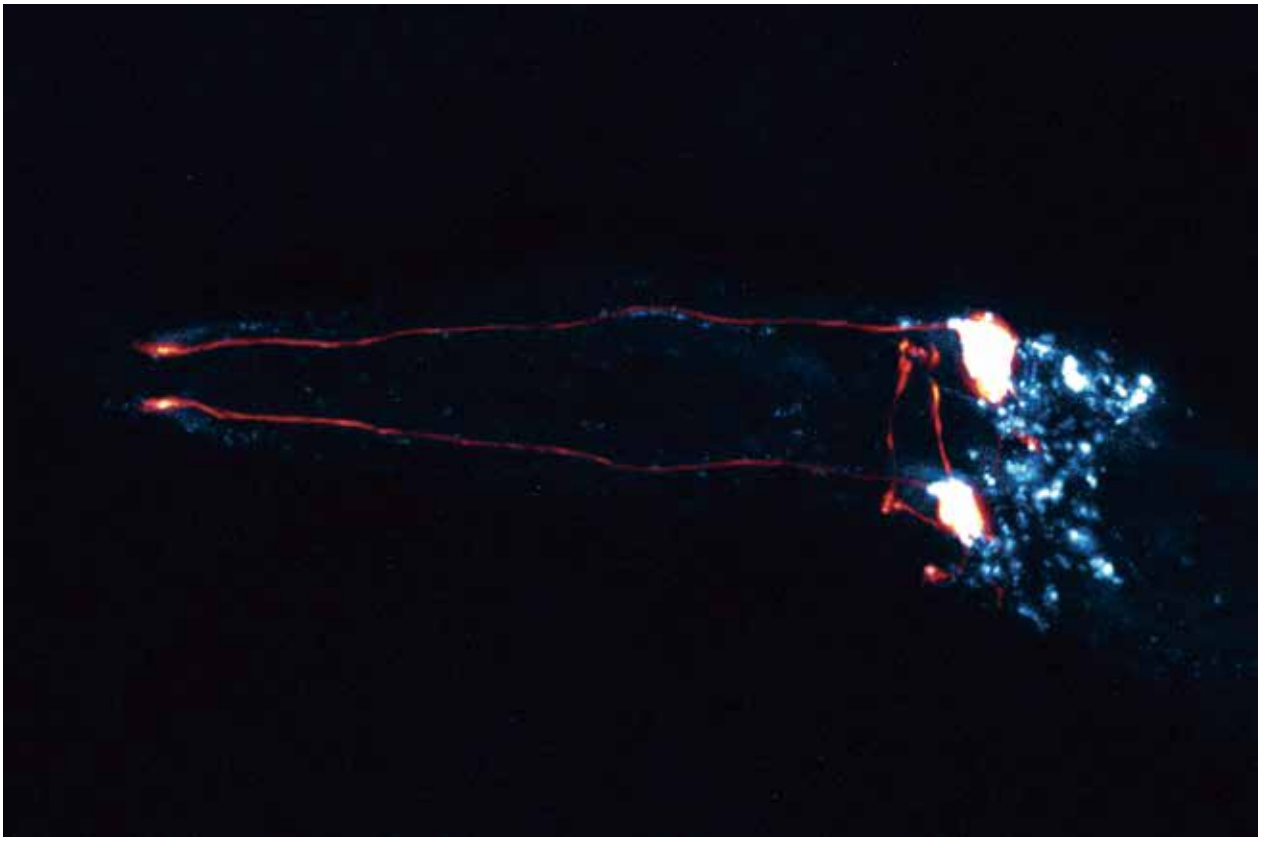
A flip of longevity with neurons

All forms of life, from those that live in the icy water of the Arctic Circle to those inhabiting the boiling hot sands of the Kalahari Desert, share one thing in common: their physiology and longevity are affected by environmental temperature. One might assume that this is simply a thermodynamic process, in which temperature alters the rates of biochemical reactions and thus establishes how quickly cells or tissues age. However, studies in a simple roundworm, *Caenorhabditis elegans*, and in mice suggest that it is the nervous system that regulates the effects of temperature on longevity. Chun-Liang Pan's group at the Institute of Molecular Medicine, NTU, recently identified key neuronal signals from *C. elegans* neurons that counteract the adverse effects of high temperature on life span.

Yen-Chih Chen and Hung-Jhen Chen, two Master's program students at the time of the study, found that AFD thermosensory neurons in *C. elegans* relay temperature information through phosphorylation of CRH-1/CREB, a transcription factor well known for its importance in neuronal memory. Formation of this putative "temperature memory" in AFD neurons leads to the synthesis of FLP-6, a short peptide, the release of which from thermosensory neurons is stimulated by a rise in temperature. Loss of CRH-1 or FLP-6 shortens lifespan, and, strikingly, an increase in CRH-1 or FLP-6 activity extends longevity at a warm temperature. Thus, modulation of a single gene overrides the unwanted aging effects resulting from a high environmental temperature.

However, thermosensory neurons do not act alone. Data suggest that the FLP-6 peptide targets AIY interneurons, which communicate with AFD neurons via chemical signals. How do a total of four neurons (two AFDs and two AIYs) globally alter the speed at which an animal ages? By profiling gene expression patterns using high-throughput messenger RNA sequencing, the Pan group found that signals from the AFD-AIY neural circuit dampen the activity of INS-7, an insulin-like peptide, as well as other genes that also engage insulin-related pathways. As activity of the insulin signaling pathway



affects the lifespan of animals ranging from *C. elegans* to primates, the finding that this thermosensory circuit counteracts high temperature by gauging the level of insulin signaling suggests that such a neural mechanism is likely a conserved theme in the sensory regulation of lifespan.

The study by Pan's group posits a provocative hypothesis whereby part of the plasticity of lifespan is essentially a physiological interpretation of the sensory environment in which the animal lives. This hypothesis also raises several intriguing questions. As the longevity of *C. elegans* at a cool temperature is also genetically regulated, it will be interesting to investigate whether a dedicated neural circuit also regulates lifespan at lower temperature as well as the neuronal signals involved in this regulation.

"The NTU *C. elegans* community (a total of seven labs) had been making great scientific discoveries over the years," said Pan as he showed his sincere gratitude for his fellow worm scientists on the campus. "For those who aim to answer big questions, starting from a humble tiny organism proves to be a fantastic idea.

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Literary men and intellectual transformations in Tang China

Literary Men and Intellectual Transformations in Tang China, by Jo-shui Chen, Distinguished Professor of History, National Taiwan University, is a major study of intellectual change in China from the eighth to the eleventh century. The subject of this book pertains to the Tang-Song transition, which is widely viewed as one of the greatest historical changes in China before the coming of Western powers in the late nineteenth century. On the intellectual side, one major outcome of this all-important transformation was the emergence of a new type of Confucianism that evolved into the cultural orthodoxy of late imperial China. This new approach to Confucianism fundamentally altered the previous intellectual order, which had been much more diverse in structure and had included key roles for both Buddhism and Taoism (mainly in the form of the Taoist religion).

In the book, Professor Chen focuses on the earlier phases of these intellectual changes, roughly, from the middle of the eighth century to the late ninth century, corresponding to the middle and late periods of the Tang Dynasty (609-907). He finds that two main strains of thought existed in the mid- and late-Tang Confucian revival. One rejuvenated the traditional form of Confucianism, emphasizing its function in establishing a sound political order. The other carried a strong anti-Buddhist sentiment and posited that Confucianism should be the guiding principle governing the human world as a whole, including spiritual matters and the cosmological significance of human existence. The former represents mainstream thought at the time, while the latter was the primary source of innovation. Professor Chen also finds that the pivotal force generating the intellectual changes in question might not have been ideas in the Confucian revival per se; rather, change was driven by the fact that many literary writers began to promote the Confucian cause after the mid-Tang era. Literary writing was the most prestigious activity in Tang elite culture, and literary writers enjoyed unrivaled status among the literati. As such, the change in focus of the literary community had an enormous intellectual impact. Professor Chen also analyzes the ideas of mid-Tang intellectual leaders in contrast to the generally held beliefs in the earlier periods of medieval China, thus illuminating both early-Tang intellectual outlooks and the essential features of the Confucian revival as an intellectual trend.

Professor Chen's book is distinctive in its approach, addressing multiple subjects related to the phenomenon of the mid- and late-Tang Confucian revival from diverse perspectives. The book is thus interdisciplinary in character. It extensively explores literary and religious trends and pays detailed attention to the social origins of ideas. Based on these diverse studies, Professor Chen offers a systematic explanation for a great and complex intellectual transition. The book not only elucidates phenomena and developments that have previously failed to receive adequate scholarly attention but also shows the dynamics—or at least some of the important drivers—of this historical change. In addition to achieving a new and expanded understanding of a critical historical shift, the book lays a solid foundation for further inquiry into the foggy intellectual conditions of the tenth and early eleventh centuries.

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Gazing into the remembrance and repentance in the Red Chamber

In the shining crown that is the history of Chinese literature, *Dream of the Red Chamber* is undoubtedly the brightest gem. The author Cao Xueqin's depths of thoughts and culture, as well as the artistic achievements of his fiction writing, have attracted the devoted attention of numerous readers, commentators and researchers. Since its inception more than two hundred years ago, we have continued to dig out the self-realized implicit or explicit profound meanings buried deep in the novel. As Lu Xun said, different minds will see different faces in *Dream of the Red Chamber*, whether love, sex, Taoism or romance, or a cultural nationalism that favors the Han Chinese and excludes the Manchu. In the present era where everyone has the right to speak, a thousand readers will have a thousand different versions of *Dream of the Red Chamber*.

However, do readers have the absolute right to interpret the novel? When we look into the depths of this gem and see the essence of *Dream of the Red Chamber*, is there still a central theme that supported and assisted the author to finish the hundreds of thousands of words during his "ten years of extraordinary hard work" and walk through his "tearful and sorrowful" journey of creation? In her book *A Grand View of The Red Chamber (General Introduction)*, Professor Li-Chuan Ou of the Department of Chinese Literature of National Taiwan University points out that the unavoidable common problems in the hundreds of years of Redology [a field of study devoted to *Dream of the Red Chamber*] were caused by our excess self-consciousness: "self-satisfaction projected in the vision of the general public." Readers do have the right to speak of history, but if they uphold the understanding that "the past and the present share unequivocally the same context," they will easily fall into the trap of "all Six Classics are my footnotes," and reading the classics will also translate into the readers' pursuit of self-positioning. They will adopt an attitude of "taking things for granted" about a world with which they have never been in contact, resulting in a misunderstanding of the distance created by self-awareness and the gap in time.

Therefore, the first introduction to *A Grand View of The Red Chamber* takes the form of a re-reading and understanding of *Dream of the Red Chamber*. Professor Ou returns to the times and social class of the author, and sets the tone of the book to be "remembrance and repentance." *Dream of the Red Chamber* is a remembrance of the author Cao Xueqin about his past experiences, but it is also, in the moment when everything has decayed, his sadness and repentance about the glory of the past.

Dream of the Red Chamber is the narrative of a woman's tragic destiny, but it is also Cao Xueqin's silhouette of the fate of his family collapse. The two tragedies are combined into one, and they reinforce each other and thus form scenes of "Qinhuai and Yangzhou are old dreams, but the people remain and have long awakened from the dreams." They are sighs and remembrances of changes in phases, and endings. This deep pain is from the destruction of a family, but it is also from the passing of youthful years, and it can be further applied from a family to the entire world. In this repeated reasoning, it brings forth a beautiful but inevitable disillusionment of the cosmos.

The author was remembering the "past" and lamenting fate. Instead of the traditional Redology discourse that takes this as criticism of the feudal aristocracy, Professor Ou believes that writing about aristocracy, which has been regarded as ironic and extravagant in the past, is in fact the beautiful memories that the author had used his whole life to write into the novel. The collapse

of paradise in *Dream of the Red Chamber* was truly built on the exclusive spiritual nobility of the true aristocracy.

Cao Xueqin had no intention of going against imperial power and ethical rituals. On a spiritual level, Cao Xueqin highly agreed with his own social class, and among the hearts of commentators who were in the same cultural circle, such as Zhiyanzhai, they also were deeply proud of their own class culture. The most basic of these is the name "Daguanyuan [Grand View Garden]"that the "Daguan [Grand View]" is a manifestation of the Confucian culture. Among the traditional culture of the elite, especially among the upper class that shared in imperial power, the Confucian culture had long been deeply rooted in its genes and souls, constructed as the basic understanding of the universe, and its ultimate concern was the practice of imperial power, which was to "have a grand view of the whole world." Therefore, the descriptions of the collapse of paradise and the "end of the world" in the novel came from the contrast between the spirits of the true "aristocracy" and their unworthy descendants. For the so-called aristocracy, in addition to their high level of financial and material enjoyment, they also needed to have character and cultivation that far exceeded those of the common people. Having received a poor education and undergone spiritual degradation, the unworthy descendants could no longer support the huge and heavy responsibility and outer shell. This was also the beginning and ending of the collapse of a century-old family, and it was also the basic tone of *Dream of the Red Chamber* as a literary work of remembrance and repentance.

Therefore, the elegy written by the author is not just about the weakness of a transcendental "human" who cannot retain his youth during the flow of the cosmos, but it was also Cao Xueqin's self-repentance about emphasizing individualism so much as to disengage from collective responsibility and unable to continue the family line and carry on the family mission. This painful projection is manifested in Jia Baoyu, the protagonist of the entire novel. Only gazing through this character on the fate of his dying family, a work of remembrance that is out of this world can be truly shown.

In an era and class system very different from today's world, the feudal and ethical code itself probably had a meaning that may be completely different from our modern understanding, and the readers must be faced with the test of accepting and respecting an alien culture. Through "*A Grand View of The Red Chamber,*" Professor Ou hopes to advocate this new understanding of the main theme of *Dream of the Red Chamber,* and this is an important message she wishes to convey to the many readers who enjoy *Dream of the Red Chamber*.

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The Ancient Greek concept of justice

In Greek mythology, the goddess Dikē (Justice) is a daughter of Zeus and Themis. She has two sisters, Eunomia and Eirene, and together they are called the Horae and embody order and harmony. Since modern times, the physical embodiment of Justice has had three main characteristics: a sword in her right hand, scales in her left hand, and a blindfold over her eyes, representing her fairness in judgement. Contemporary concepts of justice, including judicial justice, procedural justice, distributive justice, and rectified justice, are all rooted in ancient Greek political and ethical philosophy. As a virtue, justice is closely related to the idea of order and harmony in ancient Greece. To understand justice, this book therefore returns to "the original

position" to explore the ancient Greek concept of justice.

The ancient Greek notion of justice is commonly thought to have undergone a process of development; that is, it changed from a culture of shame to a culture of guilt. This book, however, challenges this traditional interpretation, arguing that different writers in different genres were all concerned with the times in which they lived and reacted to their environment through their work. Although different writers might understand justice differently, their discussion of the harmony of the ethical relationships among humans, the order of polis, the attunement of the individual soul, or even the orderly workings of the cosmos all illustrate the core idea of justice: the maintenance or recovery of an orderly state.

The discussions and arguments in this book touch on epic works, elegiac poetry, tragedy, and philosophical works and explore the notion of justice held by writers from the 8th century BC to the 4th century BC, such as Homer, Hesiod, Lycurgus, Solon, the elegiac poets, early Greek philosophers, Aeschylus, Plato, and Aristotle. Readers are urged, through the beautiful words and vivid stories, not only to grasp how the ancient Greeks understood the notion of justice and applied it to their own society, but also to reflect on their own lives and the moral and political problems we face today.

In our efforts to realize justice in our modern societies, what can we learn from the ancients? In the ancient Greek texts, we can find traces and suggestions of the elements of the successful practice of justice in moral and political life: procedural transparency, public participation, proper legislation, the principle of fairness, freedom of speech, the rule of law, the law-abidingness of citizens, and the punishment of wrongdoers.

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The choice between standard and non-standard FDI production strategies for Taiwanese multinationals

Most of the existing literature on FDI roughly divides multinational activities into two broad forms: standard vertical integration and horizontal integration. However, the production strategy of MNEs is more complex in practice. This study further classifies the production strategies of MNEs into five types (i.e., two standard and three non-standard FDI production strategies): standard vertical integration (V1), foreign concentration (V2), home concentration (V3), standard horizontal integration (H1), and heterogeneous horizontal integration (H2). This division provides more insightful implications for decisions based on the production strategies of MNEs in FDI. We then propose hypotheses addressing the role of country-level, industry-level and firm-level variables in affecting the choices between various FDI strategies.

Based on a firm-level data set of Taiwanese MNEs during the 2004–2007 period, the three sets of proposed hypotheses are, in general, supported. The main findings can be summarized as follows. First, comparing typical vertical integration (V1) with horizontal integration (H1), we find that foreign market size has a positive effect on the probability of adopting the H1 FDI strategy. This finding is consistent with most of the existing literature. In addition, we also find that the length of the overseas investment positively affects the probability of engaging in strategy H1 because "localization" enables foreign subsidiaries to be independent of their parent firms and then to produce and sell overseas. The study confirms that firm size, R&D intensity, and the export ratio have significantly positive effects on the probability of adopting V1. Our empirical results, however, show that the length of the overseas investment has a negative but insignificant effect on the probability of adopting strategy H1.

Second, we conduct a comparison between three pairs of vertical multinational strategies, i.e., vertical integration (V1) vs. foreign concentration (V2), vertical integration (V1) vs. home concentration (V3), and foreign concentration (V2) vs. home concentration (V3). The years of overseas investment experience were found to have a negative impact on the probability of engaging in V3 rather than either V1 or V2 and to have a positive impact on the probability of undertaking V2 compared with V3. This finding implies that years of overseas experience helps the formation of multinational activity V2. In addition, firm size exhibits a negative impact on the probability of undertaking V3, while R&D intensity exerts a positive impact on the selection of V3. It is intuitive to confirm that the foreign wage rate positively affects the probability of engaging in V3 compared to either V1 or V2.

Finally, this study investigates the choice between horizontal integration (H1) and heterogeneous horizontal integration (H2). Firm size is important when economies of scale can be achieved by engaging in product differentiation (Cooper and Kaplan, 1991). We argue that a larger sized firm will have a higher probability of adopting FDI strategy H2, and the empirical results support this argument. We also observe that high-tech firms tend to have a higher probability of choosing H1 over H2, confirming that firms with a specific asset, attribute or intellectual property right tend to produce some sort of exclusive products. However, foreign market size was found to have a negative impact on the probability of choosing H2. Since both strategies involve selling and producing overseas, the foreign market size and wage rate may have no crucial impact on the decision between H1 and H2 in the case of a multinational firm.

Note that the classified vertical production strategies, V1 (typical vertical integration), V2 (foreign concentration) and V3 (home concentration), implicitly indicate different stages of production and different locations. The production stages are dynamic across the three product stages: new product, maturing product and standardized product (Vernon, 1966 and Vernon, 1979). During the new product stage, production activities are

concentrated in the home country (i.e., V3, home concentration), as at this point, the producer needs more flexibility to handle the considerable amount of uncertainty in producing the new product. Production at home can offer the producer higher flexibility. Such a decision is beyond the simple factor cost plus transportation cost. In the maturing product stage, the factor cost is taken into account. To efficiently utilize and allocate resources, the producer will move the production stage that offers a lower comparative advantage in the process (e.g., the labor-intensive activity) to other countries (i.e., V1, vertical integration). As the product is standardized, the producer might move all of the production activities out of the home country (i.e., V2, foreign concentration).

As far as the governmental authority of the home country is concerned, the least desirable scenario might be concentrated foreign production, as it implies the "hollowing out" of the industry or "deindustrialization". To retain core and value-added production activities in the home country, our study suggests that instead of prohibiting or regulating outward capital movement, the governmental authority should encourage domestic firms to dedicate more resources to innovation activities, which can help them to level up technology, differentiate products and hence maintain their competitive advantage.

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Climate evolution

Geoscience researchers identified orbital forcing-controlled East Asian-Australian monsoon variability

The Intertropical Convergence Zone (ITCZ), the most important realm for the global ecosystem and human population, encompasses the heaviest belt of tropical seasonal rainfall on Earth. Due to its large rainfall gradient, a small displacement can cause dramatic changes in hydroclimate. The lack of direct long-term records, especially in the Pacific, limits our understanding of the long-term natural variability necessary to predict future ITCZ changes. A recent study by Prof. Chuan-Chou Shen of the High-Precision Mass Spectrometry and Environment Change Laboratory (HISPEC), Department of Geosciences, and his team identified the history of the western Pacific ITCZ over the past 282 thousand years. This rainfall record was published in Nature Communications on November 25, 2015, and highlighted in the journal Science on November 27.

In the study, Prof. Shen and his team generated a tropical rainfall record in the Australian monsoon territory covering the past three glacial-interglacial cycles. This record was derived from a depth profile of trace elements in the calcite shells of a shallow-water marine organism called planktonic foraminifer in a sedimentary core MD05-2925 (9°20.60' S, 151°27.54' E), which was drilled off the eastern coast of Papua New Guinea in the Southern Hemisphere.

The research demonstrates that the migration of the western Pacific tropical rainfall belt was surprisingly influenced by combined solar precession and obliquity changes, unlike the precession paradigm expressed by its East Asian counterpart. This obliquity forcing could be primarily associated with a cross-hemispherical thermal/pressure contrast resulting from the asymmetric continental configuration of Asia and Australia in a coupled East Asian-Australian monsoon system, as supported by model simulations.

Figure 1. Taiwanese and international researchers on board the RV Marion Dufresne.

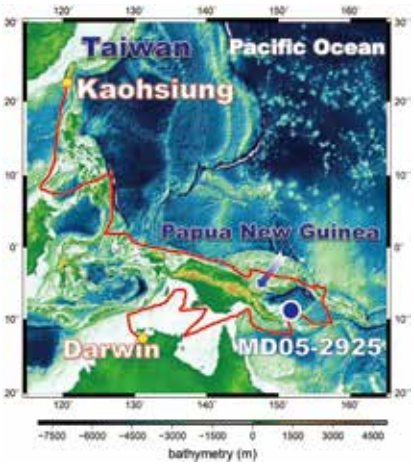

Figure 2. A 15000-km research cruise from Kaohsiung to Darwin during June 1-July 8 2005.

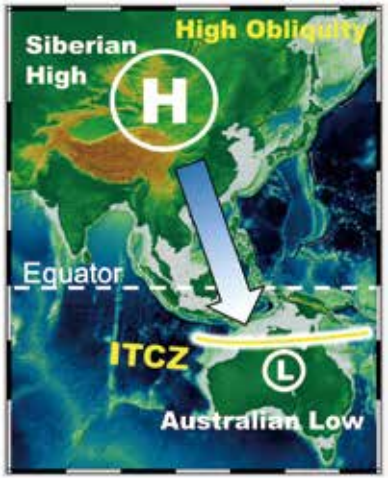

Figure 3. Illustration of the pressure-push mechanism driving the southern branch of the western Pacific ITCZ in the Asia-Pacific realm.

Figure 4. Foraminiferal carbonate shells one of natural archives documenting recent and geological-scale ocean and climate histories.

Their findings suggest that obliquity forcing may play a more important role in global hydroclimate cycles than previously thought. It also provides an in-depth understanding of the past precipitation distribution and dynamics and may offer valuable clues for future climate prediction.

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Yi Liu[#], Li Lo[#], Zhengguo Shi, Kuo-Yen Wei, Chien-Ju Chou, Yi-Chi Chen, Chih-Kai Chuang, Chung-Che Wu, Horng-Sheng Mii, Zicheng Peng, Hiroshi Amakawa, George S. Burr, Shih-Yu Lee, Kristine L. DeLong, Henry Elderfield and Chuan-Chou Shen. (2015). Evolution of the Pacific Intertropical Convergence Zone over the past 282,000 years. *Nature Communications*, 6:10018. DOI: 10.1038/ncomms10018. #These authors contributed equally to this work.

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Influences of rapid and chronic meteorological fluctuations on species elevational range size

The spatial distribution of wildlife is sensitive to climate variabilities. Classic ecological hypotheses have suggested that to adapt and become tolerant to high seasonal climatic variabilities, species in temperate mountains must survive over a greater spatial extent. Therefore, highly diverse organisms that inhabit rugged terrain in tropical and near-tropical areas have been considered more vulnerable to climate change due to the less distinct seasonality in these regions. Additionally, these organisms occupy narrower elevational ranges. However, animals are subjected not only to seasonality but also to diurnal weather fluctuations, and the latter have rarely been studied. A collaborative study conducted by researchers from Academia Sinica, National Cheng Kung University, the University of Connecticut (USA) and National Taiwan University implemented new technologies to analyze a global dataset of species distributions and to assess the

effects of a wide array of physical environmental drivers on the elevational range sizes of species.

The climatic variability hypothesis states that organisms distributed over wider geographic ranges are associated with greater climatic fluctuations. Hence, tropical mountain species are considered more susceptible to climate change than are those in northern regions since tropical species are inhabitants of a stable climate regime and have narrow elevational range sizes. However, this is contradictory to what we, as inhabitants of the region, have observed in tropical and near-tropical mountainous regions where bioclimatic variabilities are actually quite pronounced along elevation gradients. To investigate the comprehensiveness of this hypothesis, an interdisciplinary research team was formed, and it included researchers who specialized in ecology, statistics and spatial analysis. We applied structural equation modeling to investigate the relationships between global-scale climatic factors with fine resolutions and elevational range sizes for 16,000+ species of rodents, bats, birds, lizards, snakes, salamanders and frogs along 180 montane elevation gradients. The results revealed a new macroecological rule: species elevational range sizes are influenced by both diurnal and seasonal climatic variability, but in opposite ways.

Identifying the complex interactions between biotic and abiotic factors and deriving the salient variables governing species range size are critical for understanding not only the adaptation of terrestrial ecosystems in the Anthropocene but also human welfare, including the spatiotemporal dynamics of vector-borne diseases and food security. Therefore, our findings and newly postulated concept should have broad implications in the fields of biology, ecology, meteorology, public health and economics. In the past, research has mainly concentrated on the most direct and detrimental impacts of climate change on organisms, such as species extinction. A shift in the distribution of species has become apparent in the past decade, and global assessments such as the Intergovernmental Panel on Climate Change Assessment Report (Working Group 2) have mainly focused on long-term climatic trends. This study sheds new light on the relationships between animal behaviors and bioclimatic variability and adds crucial information to the current climate change literature.

The unique geographical and biophysical settings of the mountainous regions in tropical and near-tropical areas harbor a wide variety of endemic species. They are global biodiversity hotspots. Global climate change, specifically, elevated temperatures and extreme weather events, may have direct and collateral ramifications on these natural environments (the photograph shows Chilan Mountain and was taken by Cho-ying Huang in November 2015).

Their findings suggest that obliquity forcing may play a more important role in global bioclimate cycles than previously thought. It also provides an in-depth understanding of the past precipitation distribution and dynamics and may offer valuable clues for future climate prediction.

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Effects of mountain tea plantations on nutrient cycling in upstream watersheds

Although anthropogenic reactive nitrogen (Nr) increases food production to support the global population, Nr emissions due to fossil fuel combustion and fertilizer production have likely exceeded the human operational space. Consequently, the abundant Nr leaking into ecosystems through water cycling causes eutrophication in freshwater systems and dead zone expansion in coastal zones. In this study, we collaborated with a research team from the Department of Life Science at National Taiwan Normal University to monitor the streamwater and rainfall chemistry of mountain watersheds in the Feitsui Reservoir Watershed in northern Taiwan. We examined the effects of agriculture on watershed nutrient cycling and found that riverine NO_3 concentrations increased with the cultivation gradient, suggesting that agriculture-enriched fertilizer-associated nutrients are present in streamwater. Moreover, high concentrations of ions in rainfall in cultivated watersheds indicated that agriculture can influence the atmospheric deposition of nutrients and a system's ability to retain nutrients. We estimated that a tea plantation at our study site contributed approximately 450 kg-N ha^{-1} yr^{-1} of NO_3-N to streamwater, which is an order of magnitude greater than previously reported for agricultural lands around the globe. This level can only be matched in areas of intense fertilizer application. Furthermore, we illustrated the N fluxes at the watershed scale to show that excessive N leaching and additional loss to the atmosphere via volatilization and denitrification can occur under conditions of intense fertilizer use. In summary, this study demonstrated the pervasive impacts of agricultural activities, especially excessive fertilization, on ecosystem nutrient cycling in mountain watersheds.

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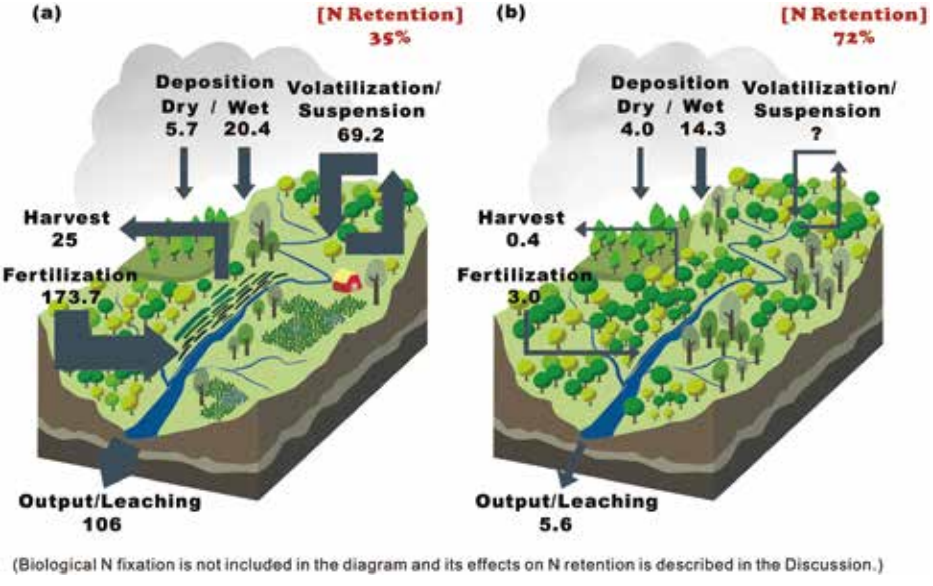

Figure 1. Schematic diagram of nitrogen fluxes in disturbed (a) and pristine (b) watersheds (units: kg-N ha^{-1} yr^{-1}).

Organic charge storage materials for high performance non-volatile organic transistor memory device

Due to increasing interest in consumer electronics, there is great demand for high-density, high-speed, long retention time (non-volatile) and low power consumption memory devices. Organic Field-Effect Transistor (OFET) memory devices have been considered to be promising candidates for next-generation non-volatile memory devices due to their non-destructive read-out properties, single transistor realization, and excellent compatibility with integrated circuits. The device shown in Fig. 1a incorporates an additional charge-trapping layer, such as metallic nanoparticles, a planar metallic sheet or polymer electrets, between the semiconductor layer and the gate dielectric layer. Fig. 1b shows the operation principle of p-type OFET memory. The p-type OFET memory is operated by applying a negative gate bias between the gate and the source electrode, where holes from the semiconductor channel tunnel through a potential barrier into the charge storage layer. The trapped charges affect the distribution of carriers in the semiconducting channel, thus resulting in shifts of threshold voltage (VTH), corresponding to the programming (PGM) or erasing operation (ERS). As a result, the digital "0" and "1" signals in one bit are determined by the erasing and programming operations, corresponding to low and high drain currents, respectively.

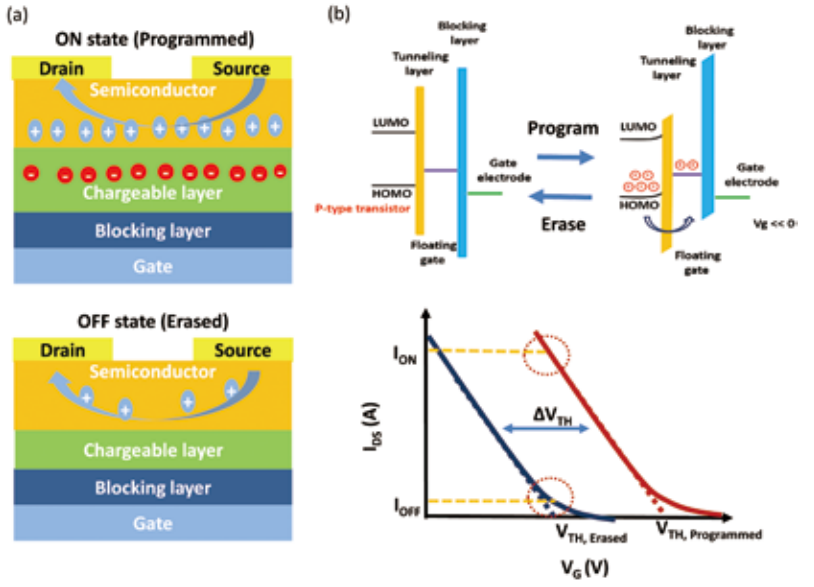

Figure 1. (a) Device structure of OFET memory; (b) Charge trapping mechanism of floating gates and I-V curve shifting in the OFET memory. (Reproduced from C. C. Shih, W. Y, Lee, W. C. Chen, Mater. Horiz., 2016, 3, 294 with permission from The Royal Society of Chemistry)

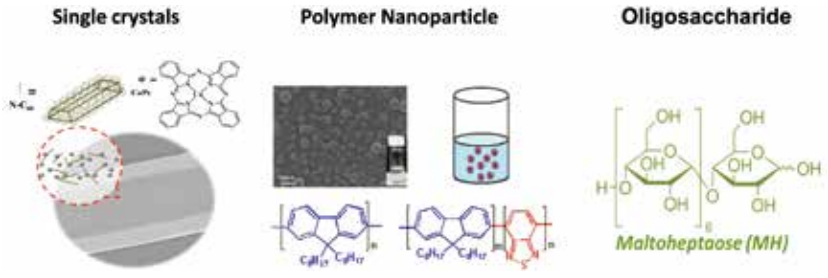

Figure 2. Three chargeable layers (nanofloating gates and renewable dielectric) developed for high-performance non-volatile memory. (Reproduced from Ref. 1, 2 and 3 with permission from John Wiley and Sons)

Precise control of the amount of charge stored in the specific floating-gate could potentially solve the fundamental scaling-down issues and meet the requirements for high-density memory devices. Recently, Prof. Wen-Chang Chen, Dr. Chien-Chung Shih, and Dr. Yu-Cheng Chiu of National Taiwan University, Prof. Wen-Ya Lee of National Taipei University of Technology, Prof. Cheng-Liang Liu of National Central University, and Dr. Redouane Borsali of CNRS, France, employed nanostructured floating gates or renewable oligosaccharide dielectrics as charge storage layers to achieve high-performance non-volatile

organic transistor-type memory, as described in the following (Fig. 2). (1) The concept of double floating-gates, bipolar charge trapping, and discrete trapping sites is first combined to develop high-performance non-volatile OFET memory. The studied double floating-gate memory could simultaneously store holes and electrons on copper phthalocyanine (CuPc) nanoparticles and needle C_{60} single crystals, respectively, leading to a broad memory window (~4.4 V), low power consumption (±5 V), long data retention time (~10^4 s), and good writing/erasing endurance (over 100 cycles). (2) A molecular nano-floating gate (NFG) consisting of pentacene-based transistor memory devices is developed using conjugated polymer nanoparticles (CPN), such as polyfluorene (PF), as the discrete trapping sites embedded in an insulating polymer, poly(methacrylic acid) (PMAA). By inserting PF nanoparticles as the floating gate, the transistor memory device reveals a controllable threshold voltage shift, indicating effective electron-trapping by the PF CPN. (3) Renewable oligosaccharides are employed as the charge storage layer in the OFET memory device because the charged hydroxyl groups facilitate the formation of strong hydrogen bonding to stabilize trapped charges and remain stable in a high-conducting state, even after successive stresses of reverse gate biases. This is the first example of employing renewable sugar-based materials as a charge storage layer that exhibit a WORM (write-once-read-many-times) memory characteristic with an ON/OFF current ratio larger than 10^6. The above results can meet the requirements for next-generation organic non-volatile transistor-type memory devices.

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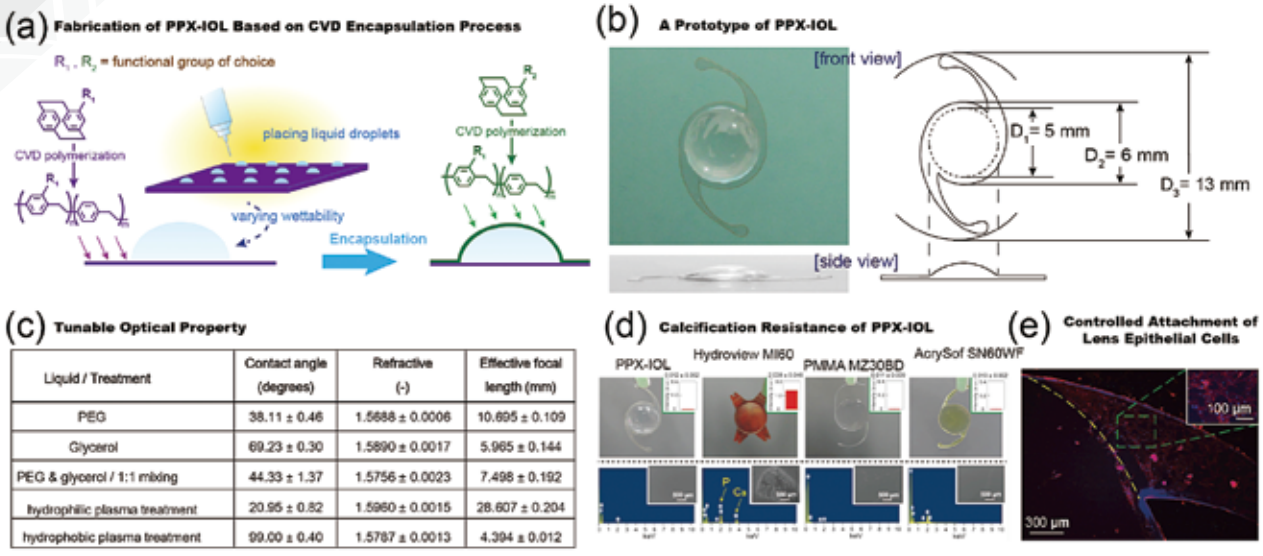
A novel intraocular lens device

The optical and biofunctional properties of anintraocular lens are customizable

The research team of Professor Hsien-Yeh Chen (Department of Chemical Engineering) at National Taiwan University has demonstrated an innovative intraocular lens (IOL) device (PPX-IOL) that is fabricated via chemical vapor deposition (CVD) encapsulation of func-tionalized poly-p-xylylenes (PPX).

The novel design of PPX-IOL provides customiza-ble parameters for both its optical and biological proper-ties. As an excellent optical device, it provides a high re-fractive index and a tunable effective focal length that is realized by manipulating the wetting properties of liquids. The device also offers protec-tion from UV radiation. As a key medical device, it exhibits excellent biocompatibility and reduced postoperative calci-fication due to the intrinsic properties of PPX. In addition, these synergistic functions provide precise surface chemistries for the placement of eye epithelial cells via guided attachment or repel-lent properties, which is very important in preventing de-vice-associated



Liquid / Treatment	Contact angle (degrees)	Refractive (-)	Effective focal length (mm)
PEG	38.11 ± 0.46	1.5688 ± 0.0006	10.695 ± 0.109
Glycerol	69.23 ± 0.30	1.5890 ± 0.0017	5.965 ± 0.144
PEG & glycerol / 1:1 mixing	44.33 ± 1.37	1.5756 ± 0.0023	7.498 ± 0.192
hydrophilic plasma treatment	20.95 ± 0.82	1.5960 ± 0.0015	28.607 ± 0.204
hydrophobic plasma treatment	99.00 ± 0.40	1.5787 ± 0.0013	4.394 ± 0.012

(a)-(b): Fabrication process and the prototype of the PPX-IOL; (b)-(e): The customizable optical and biofunctional properties of PPX-IOL.

complica-tions.

Currently, an increasing number of people suffer from cataract disease, and ap-proximately 10 million IOLs are implanted worldwide each year. There is high demand for the development of new IOL devices with properties to fulfill different optical and bio-logical requirements of each patient. The design parame-ters for the PPX-IOL device are flexible, modifications are simple, and most important of all, the optical and biological properties are customizable to a specific patient's needs. This PPX-IOL device may pave the way to the next generation of biomedical optics products.

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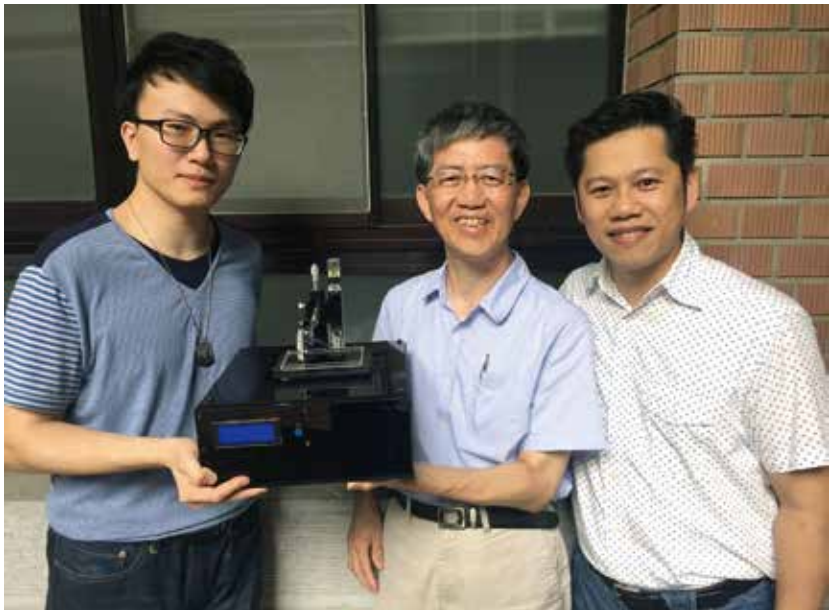
A novel western blotting device using thin-film direct coating with suction (TDCS) originally invented at NTU

Western blotting (WB) is widely used in life science studies and clinical diagnoses to detect target proteins in tested samples, such as cells or tissues, via specific antibody–antigen interactions. However, reducing both of the high material consumption costs, such as expensive antibodies, and long operation times, is still necessary to break through the WB efficiency bottleneck, especially in mass detection processes.

Intuitively, these two expectations present a dilemma because further reducing the antibody consumption would prolong the operation time and increasing the antibody concentration could decrease the operation time but increase the material costs based on the standard WB protocol. It is important to note an issue that arises in the standard protocol due to the widespread use of highly diluted solutions of primary antibodies (generally between 0.5 and 5 μg/mL to reduce material costs): millions of solvent molecules are homogeneously distributed around each solute (antibody) in the dilution process. As a result, a much longer path is formed, preventing the antibodies from contacting and binding to the antigens on the membrane. Moreover, the thicker the solution in the incubation container is, the lower the average contact probability of the antibody on the membrane becomes. This hinders the chemical reaction process and thus requires a much longer incubation time. Theoretically, gentle agitation, for example by an orbital shaker, could help to enhance the contact probability during the chemical reaction, but this would also increase the amount of antibody waste adhered on the walls of the incubation container.

Based on this analysis, keeping the membrane area constant and reducing the depth of the probing solution not only shortens the average contact distance of the antibodies to the antigens on the membrane (to enhance the chemical reaction, thus shortening the operation time) but also reduces the material consumption costs (due to the lower solution requirements). A miniaturized coater[1] for thin-film direct coating (TDC) has been developed. The μm-thin film of highly diluted antibody solution (0.04 μg/mL) was then directly and uniformly coated on the tested membrane. This novel TDC technique invented at NTU could markedly reduce the amount of antibody required for WB with an even better signal[2]. Furthermore, by using the advanced technique of TDC with suction (TDCS) to further enhance the performance, the signal-to-noise ratio of immunoblotting can be further increased, and the amount of antibody consumption can even be reduced by a factor of 100 in comparison with conventional WB. Theoretically, the corresponding operation time can be reduced from 3 hours in conventional WB to approximately 5 minutes or even less using TDCS[3]. This novel device can be applied to the high-throughput screening of antibody-drug targets, functional assays, and cell-based binding assays, as well as technology transfer for industrial commercialization.



TDCS prototype and some of the authors of the recent paper[3] (From left to right: C.-Y. Liu, A.-B. Wang and S.-C. Chang)

Reference

1. An-Bang Wang, Yu-Wen Hsieh, Yu-Ju Liu, Coating Module, TW Patent I 496625, JP Patent 5837003, 2015.
2. Yi-Kuang Yen, Yi-Wei Jiang, Shih-Chung Chang, and An-Bang Wang. (2014). Western blotting by thin-film direct coating, *Analytical Chemistry*, 86 (10), 5164-5170. DOI: 10.1021/ac5010162
3. Chao-Yuan Liu, De-Chao Lu, Yi-Wei Jiang, Yi-Kuang Yen, Shih-Chung Chang and An-Bang Wang. (2016). Easy and Fast Western Blotting by Thin-Film Direct Coating with Suction, *Analytical Chemistry*, 88 (12), 6349-6356. DOI: 10.1021/acs.analchem.6b00699

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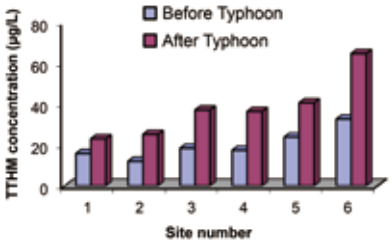
Water utilities should adapt more cautious strategies during extreme weather conditions

Behind the Scenes of Super Typhoons

Typhoons are one of the most catastrophic types of natural hazards, and they can cause severe devastation in coastal regions. Taiwan is one of the most typhoon-impacted regions in the world. The world's strongest storm in 2015, named Typhoon Soudelor, formed in the middle of the Pacific Ocean on July 20, 2015, and became more vigorous when it was well east of Taiwan over open water.



The above figure shows the mean TTHM concentrations (μg/L) in tap water before and after Typhoon Sudelor (2015) at different sampling sites with increasing distance from the source water

High turbidity in raw water in the city of Taipei and the poor quality of tap water in certain areas sparked waves of panic in the city during the typhoon event. Turbidity is not a pollutant, but it reflects the amount of sediment and organic matter in the water. High levels of organic matter in raw water negatively affect the coagulant and chlorine demands, which can increase and potentially form disinfection by-products (DBPs) that area harmful to human health.

Recently, a team led by Prof. Lo of the Graduate Institute of Environmental Engineering (GIEE) at National Taiwan University (NTU) investigated DBP concentrations in tap and drinking fountain water in selected typhoon-affected areas in Taipei before and after the typhoon. This study is important because the effects of extreme weather conditions such as typhoons and heavy rainfalls on drinking water quality are considered an issue of emerging concern, as the magnitude and frequency of such events are increasing in response to climate change.

Their results showed that organic matter increased after the typhoon event, and DBP forms when organic matter reacts with a disinfectant in pipelines. The research team further examined the effect of boiling on DBP concentrations. This was the first investigation of the effects of boiling on DBP levels in extreme weather conditions with high turbidity and organic matter loading. They found that at least 50% of THMs are removed by 2 min of boiling, whereas approximately 70% can be removed by boiling post-typhoon water samples for 5 min.

In Taiwan and most East Asian countries, typhoon rainfall accounts for a significant portion of the total annual rainfall. The research team demonstrated that the increased frequency of typhoon events can be considered one of the driving forces responsible for the global increased DOC trend.

Prof. Lo's research team generated valuable information for use by water treatment authorities in devising effective protocols for reducing DBPs under extreme weather conditions. They proved that an evaluation of the effects of climate change on annual typhoon rainfall and storm intensity is critical for water resources management and a necessary addition to climate change studies.

The study by Prof. Lo and his colleagues was published in Scientific Reports, a journal from the publishers of Nature, and made accessible to the research community on April 29, 2016.

Reference
Hoda Fakour, Shang-Lien Lo, and Tsair-Fuh Lin. (2016). Impacts of Typhoon Soudelor (2015) on the water quality of Taipei, Taiwan. *Scientific Reports*, 6:25228. DOI: 10.1038/srep25228

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Protecting topological surface states with organic monolayers

Applying topological insulators (TIs) in devices has attracted considerable interest from the scientific community due to the exotic physical properties of Tis and their potential for spintronics applications. The unique topological surface states (TSS) explicitly define the relation between electron spin and momentum. The existence of spin-momentum-locked metallic surface states makes controlling the spin signal through currents possible. In addition, electron transport through three-dimensional (3D) TIs generates a fully spin-polarized current inside the bulk bad gap. To minimize the influences on the TSS, such as electron doping and scattering, a buffer layer that forms smooth interfaces and prevents interactions between electrodes is required during fabrication processes.

We propose and demonstrate a new approach (Figure 1) that exploits an organic monolayer as a buffer layer to fabricate smooth interfaces and to prevent disturbances in the TSS during metal deposition. In our study, we use the organic molecule perylene-3,4,9,10-tetracarboxylic-dianhydride (PTCDA) to form the buffer layer on the 3D TI Bi_2Se_3 with Fe atoms as surface dopants that represent the disturbance of electrodes.

Scanning tunneling microscopy and spectroscopy (STM and STS) are used to investigate the PTCDA/Bi_2Se_3 and Fe deposited PTCDA/Bi_2Se_3 systems. In the PTCDA/Bi_2Se_3 system (Figure 2), due to the weak interactions between the PTCDA molecules and the Bi_2Se_3, the Bi2Se3 TSS is conserved on top of the well-ordered PTCDA assembly layers. By depositing Fe atoms on the Bi_2Se_3, the electron doping effect and Coulomb scattering between the TSS and the Fe atoms are addressed in the STS results. After introducing a PTCDA monolayer between the Fe and the Bi_2Se_3, the above-mentioned effects are eliminated.

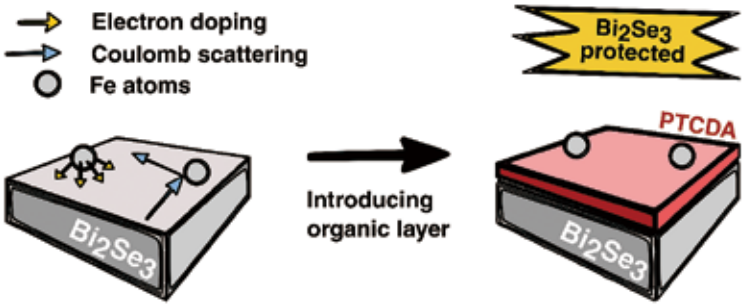

Figure 1. Illustration of the idea of using an organic monolayer as a buffer layer between the electrode and the TI surface.

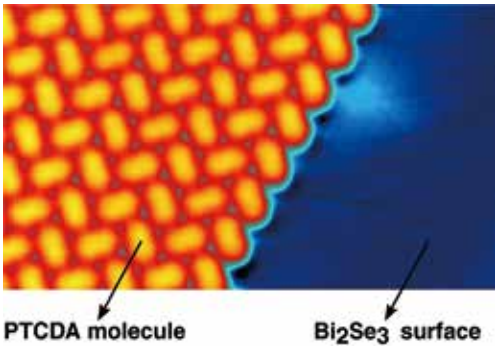

Figure 2. STM image of a self-assembled PTCDA layer on a Bi_2Se_3 surface with atomic resolution. (16×8 nm^2, V_{bias} = 1.0 V, $I_{setpoint}$ = 1.5 nA)

Our results indicate that in the presence of the PTCDA buffer layer, the Fe atoms hybridized with the PTCDA molecules instead of interacting with the Bi_2Se_3. Accordingly, the TSS is protected from the Fe deposition. Our findings provide a new approach for the construction of a buffer layer that exhibits a smooth interface and prevents interactions between dopants and TI surfaces.

Reference

Hung-Hsiang Yang, Yu-Hsun Chu, Chun-I Lu, Christopher John Butler, Raman Sankar, Fang-Cheng Chou and Minn-Tsong Lin. (2015). Organic Monolayer Protected Topological Surface State, *Nano Letters*, 15(10), 6896-6900. DOI: 10.1021/acs.nanolett.5b02811

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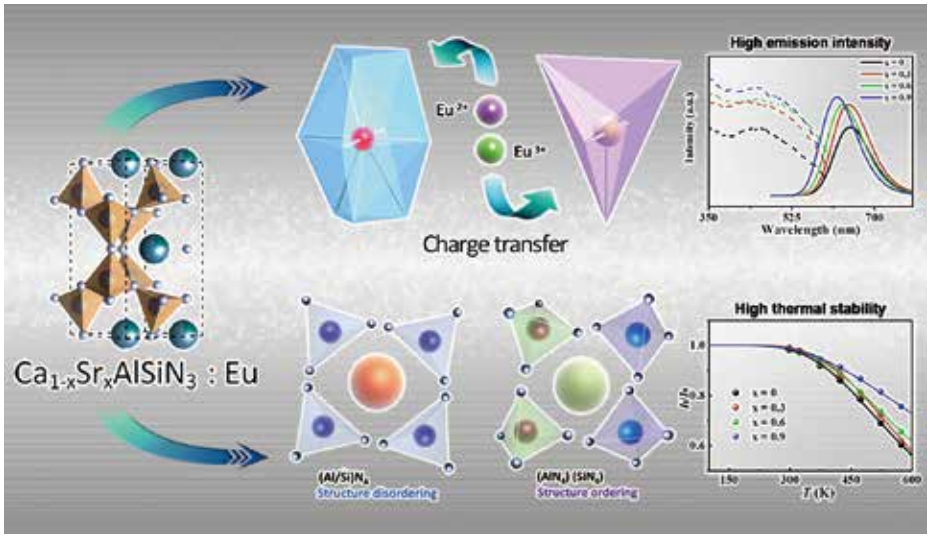
Inorganic phosphor materials for application in light-emitting diodes

Structural ordering and charge variation induced by cation substitution in (Sr,Ca)AlSiN$_3$:Eu Phosphor



Red-emitting phosphor materials have been extensively developed to increase the color rendering index and stability in white light-emitting diodes (LEDs). Nitridosilicate phosphors, such as MAlSiN$_3$:Eu^{2+} (M = Ca, Sr), exhibit high chemical and thermal stabilities because of their rigid structures. In the present study, disordering of Si/Al in (Si/Al)N$_4$ clusters is introduced in the framework via cation substitution to induce charge variation from Eu^{3+} to Eu^{2+} and simultaneously improve the thermal stability and luminescent properties of the phosphor.

The structure of the phosphor has been modified through cation substitution to induce charge variation and a rearrangement of neighboring nitride clusters and, consequently, enhance its luminescent behavior. Substitution of Ca^{2+} by Sr^{2+} cations expanded the lattice volume and the b-c plane but shortened the distance between the layers along the a axis. Lattice distortion of the framework introduced high-coordination sites in the Sr/Eu centers and adequate space, thereby facilitating charge variation of activators under reduced atmosphere, as detected through X-ray absorption near-edge structure spectroscopy. As such, the photoluminescent intensity of the phosphors increased by more than 10%, and a blueshift occurred. Cation substitution induced a special change in the anion environment, as indicated in the solid-state Raman spectra. Moreover, typical ordering variations in the SiN$_4$ and AlN$_4$ clusters are generated in the lattice. Meanwhile, neighbor sequences of (Si/Al)N$_4$ around the divalent centers were observed through solid-state nuclear magnetic resonance spectroscopy. The modified ordering distribution resulted in a rigid structure and improved the thermal quenching behavior. This study promotes the research into neighbor sequences for selective tetrahedral sites, such as Li, Mg, Al, and Si coordinated by N atoms in contact with cation sites.

In conclusion, these results not only confirm the local structure through a subtle analysis technology but also improve the phosphor properties for LED applications.

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Yi-Ting Tsai, Chang-Yang Chiang, Wuzong Zhou, Jyh-Fu Lee, Hwo-Shuen Sheu, Ru-Shi Liu. (2015). Structural Ordering and Charge Variation Induced by Cation Substitution in (Sr,Ca)AlSiN$_3$:Eu Phosphor, *Journal of the American Chemical Society*, 137(28), 8936. DOI: 10.1021/jacs.5b06080

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Reversible adapting layer produces a robust electrocatalyst

Using in situ X-ray scattering to probe the active phase for water oxidation during gas evolution

Electrochemically converting water into oxygen/hydrogen gas is ideal for high-density renewable energy storage in which robust electrocatalysts for efficient oxygen evolution play crucial roles. Recent reports of highly economical and efficient electrochemical catalysts have significantly advanced this technology. However, the largest challenge concerning the reliability of the catalyst remains unconquered. A major reason for the slow progress of reliable catalysts for water oxidation is that the electrocatalyst contains most of the charge carriers during the harsh oxidization process because the OER normally occurs under a high anodic potential. To shed light on such complex surface reactions, we need a tool that allows in situ observation of the active phase of the metal centers under anodization and a novel strategy to protect electrocatalysts under such harsh conditions in order to achieve reliable catalysts for the OER. Under practical conditions, the OER occurs only within a several-nanometer region of the catalyst surface, and in situ studies within this limited region are essential and extremely challenging.

Recently, a team led by Prof. Chen at the Chemistry Department of National Taiwan University (NTU) utilized a novel in situ X-ray diffraction method to identify a strong correlation between the initialization of the oxygen evolution and the formation of an active metal oxyhydroxide phase. The lattice of the skin layer adapts to the structure of the active phase, which enables a reversible facile structural change that facilitates the chemical reactions without breaking the scaffold of the electrocatalysts. The single-crystal nanocube electrode exhibits stable, continuous oxygen evolution for 1,000 h. This robust stability is attributed to the complementary nature of the defect-free single-crystal electrocatalyst and the reversible adapting layer.

These results add to the understanding of the phase of the active metal centers on the electrocatalysts during the reaction and the advancement of the reliability of OER electrocatalysts.

X-ray techniques provide powerful tools for the investigation of the phases of surface active metal centers in electrocatalysis and can potentially be applied to probe other catalysis systems. In practical applications, solar water splitting or artificial photosynthesis devices can be achieved via the integration of a reliable catalytic system with a photovoltaic solar cell, which captures light energy to generate sufficient driving force for H_2/O_2 generation. Prof. Chen remarked, “This study can serve as a new strategy to realize the behaviors in liquid media and to design robust electrocatalysts for artificial photosynthesis that allow for the conversion of sunlight into oxygen and chemical fuels.”

Prof. Chen’s group is also currently working on developing novel in situ methodologies to realize the mechanisms behind the reactions. In the future, these strategies can be applied to achieve artificial photosynthesis.

Reference

Ching-Wei Tung, Ying-Ya Hsu, Yen-Ping Shen, Yixin Zheng, Ting-Shan Chan, Hwo-Shuenn Sheu, Yuan-Chung Cheng, Hao Ming Chen*. (2015). Reversible Adapting Layer Produces Robust Single-crystal Electrocatalyst for Oxygen Evolution. *Nature Communications*, 6:8106. DOI: 10.1038/ncomms9106

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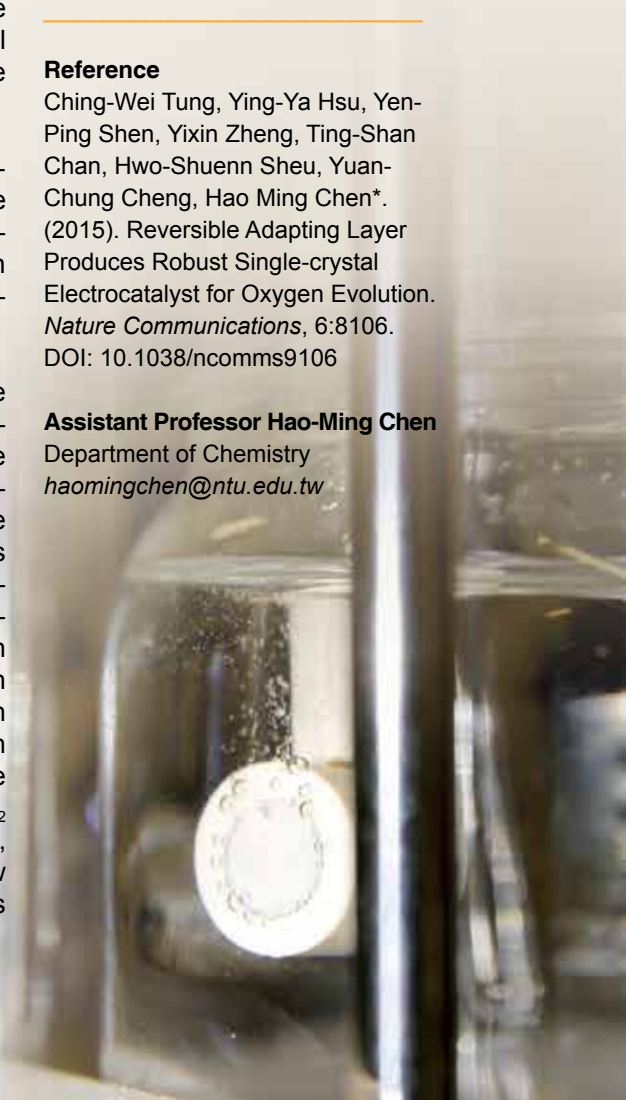

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Cover
Ocean Researcher I to deploy the observation buoys at the end of June, 2016. Led by Prof. Yiing-Jang Yang, the team chose to position the buoys 175 kilometers to the east and 375 kilometers to the southeast of the southern tip of Taiwan. Within a week of the deployment, Typhoon Nepartak formed and began to develop into a super typhoon as it veered towards Taiwan, the buoys moored directly in its path. Join our discussion about climate change on page 4.

LANDSCAPE
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Issue 2 January 2017

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ISSN 2518-4326
GPN 2010501304