SPOTLIGHT

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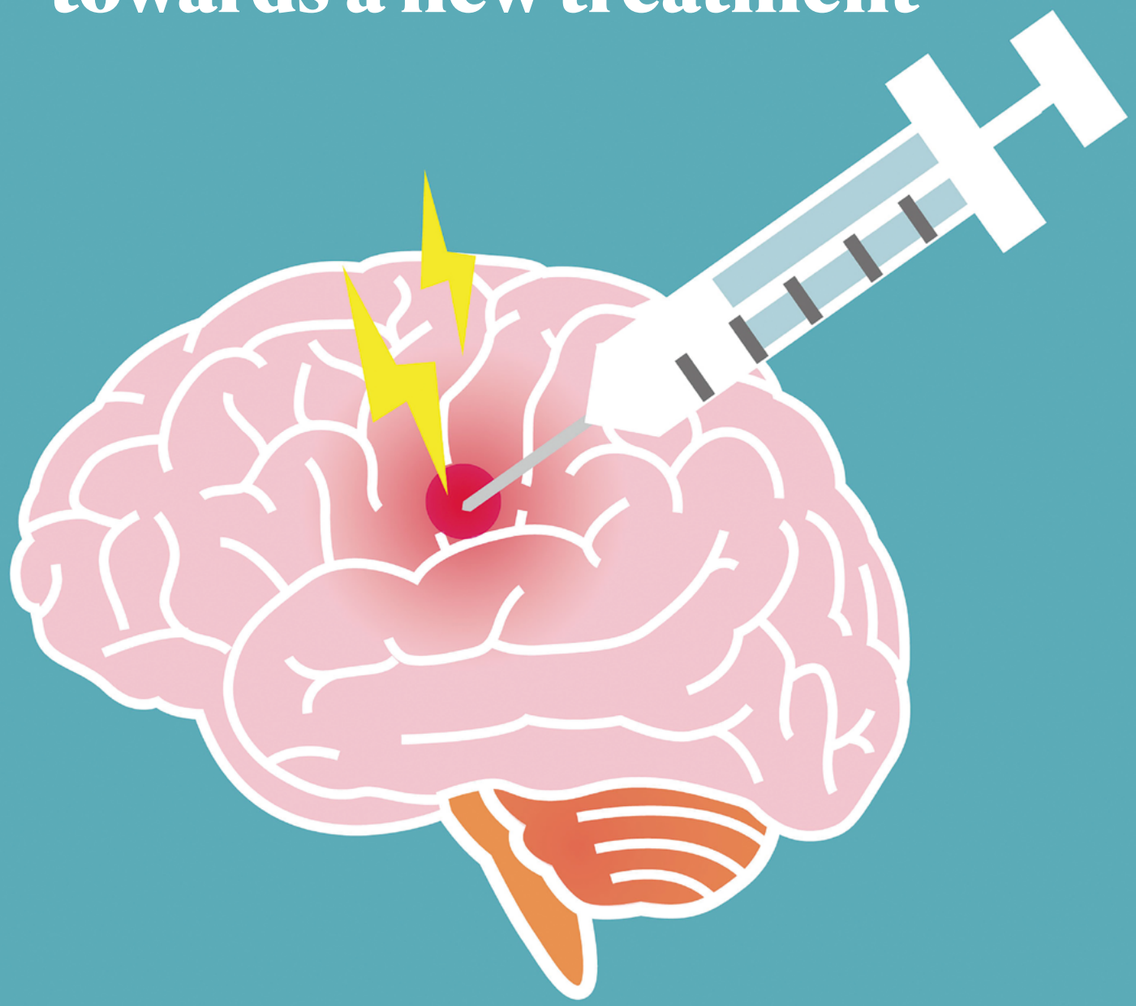
Head trauma: towards a new treatment



Traumatic brain injury due to road traffic accidents, sport injuries, falls, or military casualties, is a major and growing cause of disability and death worldwide. TBI induces an immediate mechanical damage followed by detrimental chain of secondary side-effects promoting neurodegeneration. There is no treatment providing both short-term neuroprotective action or long-term neurorestorative therapy. An international collaboration (NeuroTMULille international laboratory) between Taipei Medical University (Ouada Nebie, Thierry Burnouf) and Lille Neuroscience & Cognition (David Blum, David Devos, Luc Buée) just published in the journal "Brain" that the complex pathological consequences of TBI can be alleviated by the delivery of a Human Platelet Lysate (HPL) specifically formulated for brain administration.

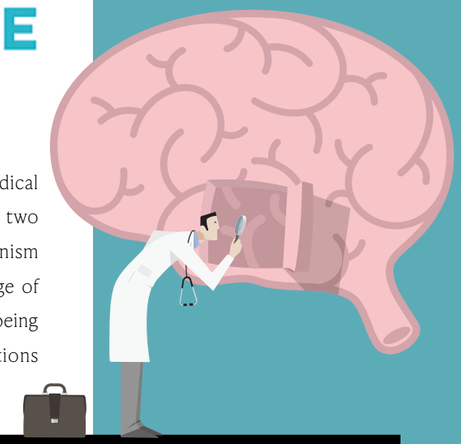
The published work demonstrated that HPL improved motor function, mitigated neuroinflammation and oxidative stress in the injured cortical area and reduced synaptic alterations in two mouse models of TBI. "This platelet biotherapy would represent a treatment addressing the multiple physio-pathological causes of TBI and avoid progression towards neurodegenerative processes" David Blum commented on the findings.

HPL are composed of a balanced composition of protective neurotrophic factors with the capacity to activate multiple biological protective pathways and represent a novel therapeutic approach in regenerative medicine. They are prepared from platelet concentrates collected by whole blood donations or apheresis procedures from healthy donors. Platelet concentrates, the source of the human platelet lysates, are essential medicine according to the WHO, and are available worldwide, meeting stringent quality and safety criteria in many countries. "Our results suggest the importance of a careful formulation of human platelet lysates to ensure optimal safety and efficacy for brain administration. The potential, yet to be confirmed in humans, to deliver this product by the intranasal route opens extremely exciting prospects in the treatment of neurological diseases. Our results suggest the importance of a careful formulation of human platelet lysates to ensure optimal safety and efficacy for brain administration. It is now vital to move into further pre-clinical assessment and carefully controlled and monitored clinical studies" commented Thierry Burnouf.

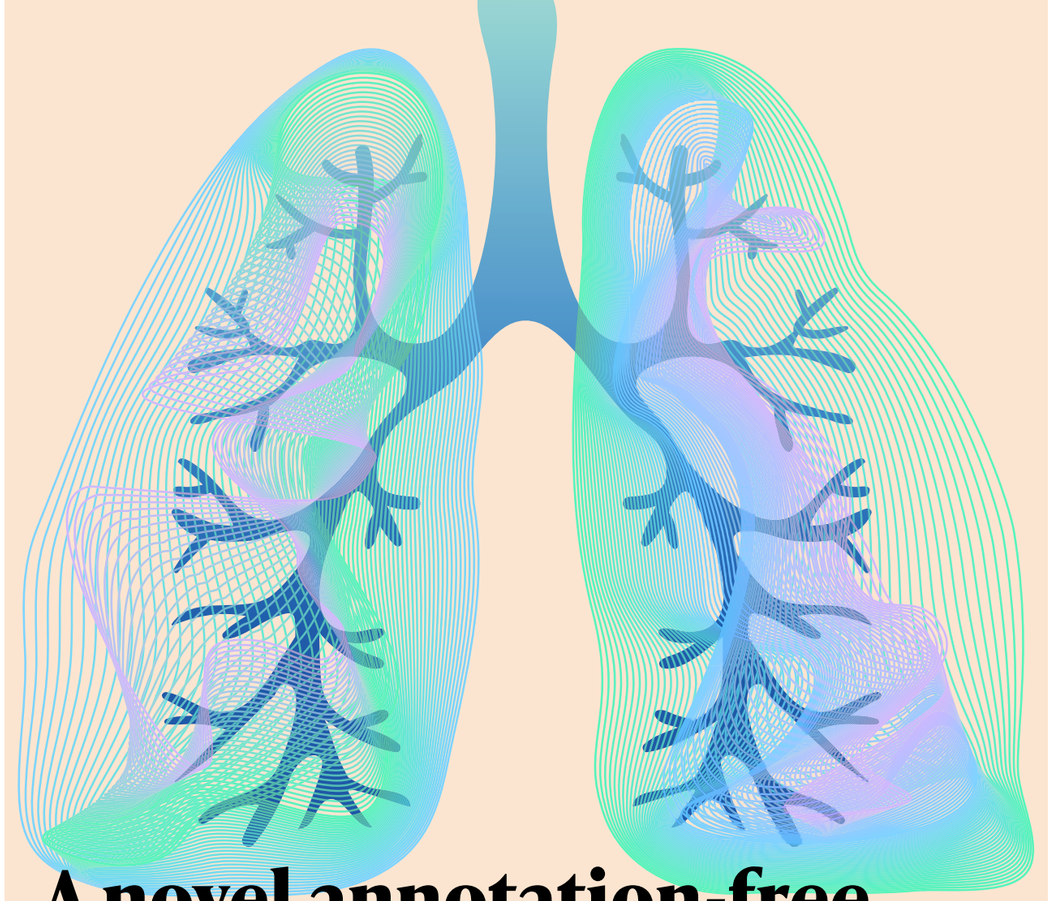
NEURO TMULILLE

NeuroTMULille

NeuroTMULille is a joint neuroscience laboratory established by Taipei Medical University and the University of Lille in 2019. Through NeuroTMULille, the two institutions are currently moving forward to introduce a seed fund mechanism and identify collaborative research teams from both sides. Bilateral exchange of researchers and students, as well as dual degree programs are continuously being implemented to further strengthen the international research collaborations between the two institutions.



Reference:
Human platelet lysate biotherapy for traumatic brain injury: preclinical assessment.
Nebie O, Carvalho K, Barro L, Delila L, Faivre E, Renn TY, Chou ML, Wu YW, Niem-Redene A, Chou SY, Buée L, Hu CJ, Peng CW, Devos D, Blum D, Burnouf T. Brain. 2021 Jun 4:awab205. doi: 10.1093/brain/awab205.



A novel annotation-free whole-slide classification of lung cancer pathologies

The annotation-free whole slide training approach is superior to the multiple-instance learning in classifying non-small cell lung cancer subtypes.

Original Research Article:

An annotation-free whole-slide training approach to pathological classification of lung cancer types using deep learning

DOI: https://doi.org/10.1038/s41467-021-21467-y

In nonsmall-cell lung cancer (NSCLC), proper pathological diagnosis to differentiate between adenocarcinoma and squamous cell carcinoma presents a challenge, as the difference in pathological features between them is subtle. CNN has been the primary method used in image recognition in distinguishing these two histologically different NSCLC subtypes. Despite its success in tumor type identification and classification, the patch-based CNN method demands substantial annotations on the slides by experienced pathologists. Multiple-instance learning (MIL), another previous technique employed to reduce the annotation burden, on the other hand, is subject to incorrect selection of patches for diagnosis or classification in early training leading to compromise in the model's performance. To overcome the limitations of existing methods, a group of researchers from Taipei Medical University (TMU) proposed the use of whole slide imaging (WSI) as means to train CNN utilizing slide-level labels. Based on the outcome, the WSI method is proven to be superior to the existing methods of digital diagnosis, specifically in comparison to the MIL method.

For the purpose of establishing an optimum approach for pathological classification of lung cancer subtypes, these researchers developed a annotation-free whole slide training method to train CNN. The design consolidates unified memory (UM) mechanism and some graphics processing unit (GPU) optimization technique to train standard CNN with much bigger image input without compromising training pipeline or model architecture. A total of 7,003 slides were gathered, consisting of 2,039 cases of non-cancer, 3,876 of adenocarcinoma and 1,088 cases of squamous carcinoma, then randomly assigned for training, validation, and testing purposes. Subsequently, the slides were tested using multiple performance models to study different parameters in image analysis in lung cancer. As a result, the WSI method used recorded superior results to MIL in visualization, small lesion diagnosis, image resolution (despite data size), and memory consumption. Such superiority is attributed to two things, the randomness of the sampling and the existence of ceiling to the performance of MIL due to the lack of ground truth at patch level. Therefore, a heftier sample size might be required in future research in comparing the two different models. Provided that there is also a limitation on host memory when training larger images on CNN, future research on a more memory-efficient algorithm will further optimize the model in digital diagnosis of diseases.

First introduced in 1999, WSI has achieved remarkable growth in technology and is recognized in various applications in pathological diagnosis ever since. The approval of the US FDA to a WSI system for primary surgical pathology diagnosis in 2017 has paved the way for the acceptance of this technology for broader medical applications. The application of AI in pathology is most often limited by the constrain of annotation that retards the process pace due to its focus at a microscopic level. The method explored in this study can counter that disadvantage by providing rapid progression via reduction of meticulous annotation. Given that the healthcare demand is increasing by the day, non-laborious, highly efficient technology is snatching importance in enhancing diagnosis and disease classification processes. Thus, the utilization of WSI to train CNN in the diagnosis and classification of lung cancer becomes imminently crucial and contributes to the realization of United Nations' Sustainable Development Goal 3 (Good Health and Well-being). Given the promising future advancement of WSI technology and numerous benefits, WSI should be adopted and prioritized for its application in the healthcare sector by authority bodies and investors. Considering that cost is a current limitation for its implementation, a more cost-effective WSI should be developed to facilitate the medical fraternity to contribute to the overall healthcare improvement of the global community.

References

1. Kumar N, Gupta R, Gupta S. Whole Slide Imaging (WSI) in Pathology: Current Perspectives and Future Directions. Journal of Digital Imaging. 2020;33(4):1034-40.
2. Saha S. A Comprehensive Guide to Convolutional Neural Networks — the ELI5 way. 2018.

Dr. Cheng-Yu Chen

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Using weather patterns to predict dengue outbreaks

Fluctuating climates significantly impact dengue transmission and can serve as a useful early warning mechanism to predict future dengue outbreaks.

Original Research Article:

Effects of local and regional climatic fluctuations on dengue outbreaks in southern Taiwan

DOI: 10.1371/journal.pone.0178698

Climate change has constantly made headlines, not just in the forms of hot debates but also through calamitous events such as blizzards, hurricanes, flash floods, and heatwaves. Climate change consequences have often been painted with the image of melting glaciers and rising sea levels. However, there are deadlier problems breeding right in our backyards. Long back in 2000, the World Health Organization (WHO) published a bulletin predicting the average global temperatures to rise by 1.0 to 3.5°C by 2100. As a repercussion, it stated climate change-driven alteration of the temperature, precipitation, and humidity is expected to affect the biology and ecology of a range of organisms. Researchers feared that a spike in vector population and the risk of disease transmission are almost inevitable. It is concerning as vector-borne diseases such as dengue, malaria, yellow fever, Lyme disease, plague, and leishmaniasis kill over 700,000 people globally each year, with most cases found under tropical and warmer climates.

Dengue fever is among the commonly transmitted vector-borne diseases in tropical and subtropical regions. *Aedes* mosquitoes are the primary vectors responsible for the transmission where *Aedes aegypti* is the leading cause for urban dengue infection while *Aedes albopictus* is mainly associated with cases in rural areas. According to WHO, the rate of dengue infection worldwide has increased significantly in recent decades, and around 100 to 400 million infections are being reported each year.

The impact of climate change on public health has been long recognized. Consequently, several interventions and policies to mitigate climate change have been set in motion in the national and international regions. In many situations, the epidemics and deadly consequences of these climate variabilities on the health of the human populations exposed can be prevented and controlled by developing adequate surveillance and preparedness tools. Existing dengue control prevention and management is ineffective as it is only initiated upon receiving reports of locally acquired human cases. Hence, making it a step too late in controlling the vector propagation and virus transmission from the very beginning. Such lack of a reliable early warning mechanism inspired a group of researchers from the Department of Molecular Parasitology and Tropical Diseases at Taiwan Medical University (TMU) to develop a climate-based forecasting model as a solution.

The geographical positioning of Taiwan, placed in the northern edge, makes it highly unlikely to experience dengue outbreaks all year long compared to its Southeast Asian neighbors. However, it has been a victim of imported cases, mainly from international travelers in spring, leading to local outbreaks during subsequent summer and fall. The rate at which the disease transmits locally is theorized to result from the regional environment and climate conditions. A number of past studies did associate factors such as temperature, relative humidity, and precipitation with dengue transmission. Yet, no firm prediction model based on these parameters has been used to give out early warning alerts.

In 2014 and 2015, Taiwan experienced unprecedented dengue outbreak incidences, but the cause remains unclear, especially in terms of its association with climate fluctuation. Till today, events of this scale remain a burden for public health personnel to implement the best control and prevention measures. On the bright side, the epidemiologists of TMU believe that an effective dengue early warning system is just a stone's throw away from establishment. Climate variability could be the key to it all. They hypothesized that the transmission is influenced by interannual climate variations that affect mosquito ecology and subsequent dengue virus transmission. Since climate, vector ecology, and social economics vary from one continent to another, it brought about the need for a regional analysis of the local transmission cause. As a result, two major dengue hotspots, Kaohsiung City and Tainan City, and their local and regional weekly minimum temperature were identified as a reliable indicator for predicting disease transmission. Apart from that, the association between regional climate phenomena (El Niño-Southern Oscillation (ENSO) and Indian Ocean Dipole (IOD)) and dengue inter-annual outbreaks were investigated along with the monthly data of the local climate parameters.

Analysis of the reported dengue cases and climatic conditions of the two hotspots concluded that temperatures higher than 23°C is optimal for mosquito development and virus propagation. With high temperature, the mosquito life cycle accelerates, increasing the mosquito proliferation rate. At the same time, the virus gets to replicate much faster within the mosquito, shortening the time required for the mosquito to become infectious. On the other hand, increased rainfall or precipitation may decrease the temperature, but it increases the chances of water puddle formations favorable for mosquito breeding. With more people choosing to stay indoors during the wet season, the probability of contact and the risk of infection increases. These effects are predicted to last up to 10-15 weeks.

In conclusion, implementing improved outbreak prediction and detection through coordinated epidemiological and entomological surveillance is among the few ways to reduce dengue morbidity effectively. The climate-based predictive model for dengue early warning alert developed by this research is capable of providing reliable forecasting results 6 weeks ahead of the outbreak. With this, healthcare personnel and public health decision-makers are given sufficient timeframe to initiate timely preventive measures to reduce the rate of dengue infection as well as prevent a higher death toll. By extension, a similar climate-based forecasting model could be applied to predict the risks of other vector-borne disease transmissions such as Zika and Chikungunya. Essentially, the development of such an early warning model would contribute towards Taiwan's effort in realizing the United Nations' Sustainable Development Goal 3 (Good Health and Well-Being), to reduce premature mortality from non-communicable diseases through prevention and treatment. Likewise, it is a tool necessary to strengthen resilience and adaptive capacity to climate-related hazards, in this case, vector-borne disease transmissions, not just in Taiwan but also to support other countries facing similar threats. Thus, amplifying the usefulness of this development in fulfilling some of the crucial targets of the United Nations' Sustainable Development Goals 13 (Climate Action) and 17 (Partnerships for the Goals).

Dr. Ting-Wu Chuang

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Joint-Appointment Associate Professor, Master Program in Applied Molecular Epidemiology

Joint-Appointment Associate Professor, School of Public Health

From bench to business: the translational road of a female scientist

Professor Wei-Chung Yang has come full circle. A graduate of TMU's undergraduate College of Nutrition, she is now Professor in the Program for Translational Medicine and the Graduate Institute for Biomedical Informatics, and founder of the biotechnology startup V-Check, Inc.

Yang's scientific curiosity has motivated her from a young age. As a high school student, she read issues of *Scientific American* and biographies of scientists, including that of Marie Curie, who she still describes as "my idol." During her undergraduate studies, she chose to go to Academia Sinica for a summer student program, where she learned about cell culture and other basic lab techniques.

Having built her foundation in biology in Taiwan, she enrolled in the University of Texas Health Science Center for an interdisciplinary PhD program. Yang reflects that the freedom students were given there to design a program of study was "very good, because we could have a broad scope to try to solve the questions we wanted to ask." She worked with a mentor to investigate the extracellular matrix, a network of attachments surrounding cells that may regulate cells migrate to other tissues, a process that occurs in events as fundamental as embryogenesis or pathogenesis as cancer cell metastasis.

After a postdoctoral fellowship at Academia Sinica, Yang returned to TMU to join the faculty and took on the challenge facing all fresh professors: applying for her first research grant. Although one possible avenue for her research was to investigate the role of the extracellular matrix in cancer development, competition in this area was fierce. Savvy, she decided to take a different approach. Turning to the unique environment at TMU, which offers

opportunities for extensive opportunities for interactions between clinicians and basic scientists, she got to know many medical doctors from different specialties. That led to her learning about endometriosis, a condition in which endometrial tissue grows outside of the uterus, which can result in ovarian cysts, chronic inflammation in the pelvic region, and infertility. She realized there was a need for research into endometriosis, and a potential for improving diagnostic methods for endometriosis. Up until now, the standard for diagnosis remains a surgical procedure called laparoscopy followed by histopathological analysis. "Women are very hesitant to accept that diagnostic procedure," Yang says. "A lot of women notice they have endometriosis from [first going to the clinic for] infertility. If they hear they need invasive technology to confirm this, they will back up – ten miles away!" She realized the need and the fit with her basic research interests and successfully applied for her first grant with this topic.

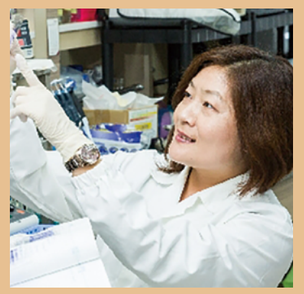
Yang spent the next several years carrying out basic research in endometriosis. Simultaneously, she developed her knowledge of endometriosis in the clinic, joining doctors in reproductive medicine for daily morning meetings, collecting clinical samples, and studying medical records, procedures, and patient concerns. Then in 2015, she was awarded what she refers to as "an unusual research grant" from the Ministry of Science and Technology (MOST), it provides seed money to support a research team with innovative technology to become a startup. (Research grant name in Chinese: 應用型研究育苗專案計畫) Although MOST grants usually provide funds for only scientific research and not company-related (commercialization) purposes, this grant was a "seeding fund" with the explicit goal of helping basic scientists start companies in order to turn their innovative discovery from basic research into real products. Yang's lab was specifically scouted for the grant, with a MOST-assigned team spending time in her lab over the course of a year to evaluate the quality and maturity of her research, which set off her journey to entrepreneurship.

Basic science research and entrepreneurship can be complementary, but also require different skills and the ability to adapt to the unique requirements of each. "Different brain! … I need some time to wash my brain [when going] between academics and industry," Yang says. Elaborating, she describes how "we can ask hundreds of questions in research, and you can explore whatever you are interested in – but for a product,

there is something you need to follow, you have to follow clinical guidelines, regulations, ISO guidelines, and you also have to think about patents."

A notable source of support during this transition has been the BioLadies group, founded by fellow women biotechnology entrepreneurs Grace Yeh and Jo Shen. Its members include those with expertise in pharmacy, basic research, accounting, and finance. The group shares information on LINE, and even has different "subgroups" – including a choral subgroup, and a book reading subgroup, which recently discussed John Carreyrou's *Bad Blood: Secrets and Lies in a Silicon Valley Startup*. With the challenges of balancing the multiple demands of research, entrepreneurship and family life, Yang says that "in the BioLadies group, we have the same questions and challenges so we can share our experiences in the group."

Meanwhile, Yang's startup is currently raising Series A funding for clinical trials of its inaugural product. Yang hopes that as V-Check continues to grow up and become established, she can continue to do research and develop new products to make further contributions to women's health. She is also passionate about helping future budding entrepreneurs. Taiwan is well known for its IT industry, but the structure for biotechnology development is not as well established, and biotechnology products often require a longer period of investment and growth. She points out that the support of TMU has been critical for the success of V-Check, allowing her space to contribute her time to both her academic research and her entrepreneurship endeavors. She hopes that her story will encourage universities and the government to continue to support future biotechnology startups, and also encourage young faculty members with an eye towards entrepreneurship to begin to "cook" their studies: "Because we are all in the field of biomedicine, we are doing research with benefit to patients. If it is a good discovery, it has to become real."



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TMU's international students initiate beach cleanup to protect the ocean from garbage

A group of TMU international students voluntarily cleaned up the beach in Northern Taiwan, hoping that through their personal effort, they can help improve environmental and marine ecology protection while at the same time increase public awareness of environmental protection and reduce marine pollution.

The initiator of the beach cleanup is Elizaveta Parfenova (Liza for short) from Russia. Liza is a second-year doctoral student at the Graduate Institute of Mind, Brain and Consciousness (GIMBC), College of Humanities and Social Sciences. Liza said that environmental protection has being part of her daily life because of the influence of her parents since she was a child. In 2020, she joined SCUBAR, a scuba diving association, in a beach cleanup in Fulong Beach. Back in school, she responded to her teacher's call to take action in plastic reduction, and decided to recruit her classmates, colleagues and teachers for beach cleanups.

To date, students from many countries have responded, including those from the United States, Russia, Spain, Indonesia, India, Chile, Estonia and Taiwan. They would go to Fulong Beach once a month to clean up. A large garbage bag can hold up to 20 kg of garbage. Generally, each student can fill up to 6 bags in one cleanup. With the number of students participating in each cleanup increasing, more and more marine debris is being cleared out.

Most of the garbage is plastic, such as PET bottles and fishing gears. Others include discarded utensils, broken porcelain plates, lighters, slippers, as well as fishing nets, styrofoam and other large waste items. Even animal carcasses have been found.

Philip Tseng, Vice Dean of the TMU College of Humanities and Social Sciences, pointed out that College of Humanities and Social Sciences has numerous environmental protection code of conduct. For example, disposable tableware and plastic products are not encouraged. Mugs are also available in the College so that students can avoid using disposable paper and plastic cups. Many of the teachers and students turn on only the desk lamps at their seats when they use their offices and laboratories to save energy and reduce carbon emissions. To mitigate the impact of global warming, the College offers only vegetarian food and encourages students to reduce plastic and be aware of the environmental impact of their diet.

Liza also tries to lead by example at school by promoting a low-waste lifestyle. For example, she tries to buy second-hand clothes instead of new one whenever possible, as well as not buying things that are not necessary or disposable. Additionally, Liza usually chooses to buy unpackaged fruits and vegetables, and provides her own containers for take-out food. She also tries to minimize animal products as much possible due to their

environmental harm. “These "little things" in daily life are concrete actions for a low-waste life” Liza said.

Vice Dean Tseng said that for an international student to come to Taiwan and be able to spontaneously involve herself in sustainable lifestyle promotion and eco-friendly beach cleaning activities is not an easy feat. To encourage students’ beach cleanup activities, teachers would privately support the transportation expenses out of their own pockets. In the future, teachers and students will be invited to share their philosophy on beach cleanup to 1) attract attention to marine environmental problems, 2) share environmental information and suggestions based on scientific evidence, and 3) call on more people, especially those who can make changes in policies, to protect the environment.

Risa, a fellow student from Indonesia, said that after participating in the beach cleanup activities, she began to learn more about marine environment pollution and the harm suffered by marine organisms. Cleaning up beaches has not only allowed her to contribute her part to the environment, but also helped her extract herself from her busy graduate student life and recharge her body and mind.

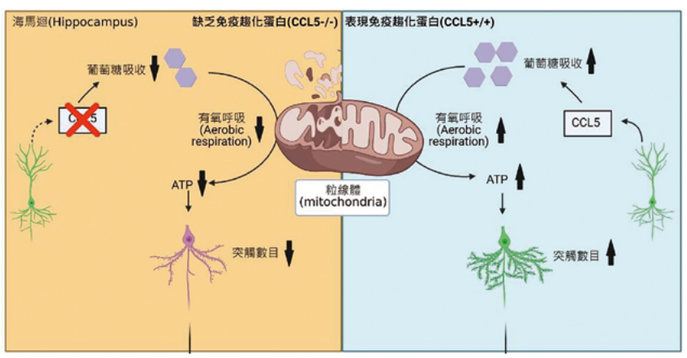
New hope for Alzheimer's treatment: TMU leads the world in new discoveries with publications in internationally renowned journals

The global Alzheimer's population continues to rise rapidly. The Taiwan Alzheimer's Disease Association estimates that one out of every 80 people has dementia in Taiwan. According to the Alzheimer's Disease International (ADI), the global Alzheimer's population will grow up to 152 million people by 2050. This means that there will be one person suffering from Alzheimer's in every 3 seconds; no effective medicine has been found in current

A research team comprising members from Taipei Medical University, the National Health Research Institutes and the Tri-Service General Hospital has found that immune chemokines (CCL5) can regulate the activity of hippocampal neurons in mice to improve the memory circuits formation, as well as learning and memory ability. This research was recently published in the top neuroscience journal, *Molecular Psychiatry*, under the world-renowned *Nature* series.

Associate Professor Szu-Yi Chou from the Ph.D. Program for Neural Regenerative Medicine at TMU pointed out that 90% of the CCL5 expressed by neurons in the hippocampal gyrus, where is response for memory formation. Study found that CCL5 greatly affects the aerobic metabolism in neurons and contributes to memory-cognition performance in mice. This suggests that CCL5 plays a pivotal role in the regulation of neuronal energy and affects the immediate energy supply during the process of memory formation.

Associate Professor Chou reiterated that a direct use of immune chemokines for treatment may bring high risks and is therefore not the best solution. Future research mainly further identify applicable drugs that are based on the mechanism, such as finding safe drugs that can increase the function of CCL5 in order to achieve the effect of improving learning and memory.



↑ The research found that the lack of immune chemokines affects brain memory and learning ability. The diagram on the left shows decline in learning and memory, and the diagram on the right shows increase in learning and memory.

↑ Associate Professor Chou from the Ph.D. Program for Neural Regenerative Medicine at TMU.

↑ Associate Professor Chou (3rd row, 1st on the right) and the research team.

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