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China Medical University
Newsletter Issue #3

“Leading Cutting-Edge Care, Mastering Future Health” China Medical University and Healthcare System participated in the 2019 Taiwan Healthcare+ Expo



The 2019 Taiwan Healthcare+ Expo had three main themes: “Smart and efficient healthcare,” “New horizon of cancer treatment,” and “New generation of gene technology.” During the Expo, President Mien-Chie Hung emphasized the vast research of CMU, and the research centers established to study tumors, immunology, stem cells, Chinese herbal medicine, Chinese medicine & acupuncture, brain diseases, and aging. He also mentioned that CMU has been actively recruiting outstanding faculty members, doctors, and research teams, and has been cooperating with prestigious medical centers and research institutions to develop advanced medical care.

Five CMU research teams and spin-off companies of CMUH received the 2019 National Innovation Award. The five awards were in: 1) HLA-G CAR Immune Cell Therapy, 2) The Smart Health Technology Category, 3) Innovative Cell Blocks for 3D Artificial Dermis Development, 4) Precision Serological Diagnosis Kit for Rheumatoid Arthritis, and 5) Dental Intra-Oral Computed Tomosynthesis System.

Highlights of CMU and CMUH in the “2019 Taiwan Healthcare+ Expo” include:

1. Cell Therapy Center: The first and only medical center to provide Dendritic Cell (DC) therapy for all stages of 8 major cancers in Taiwan.
2. Center for Precision Medicine: Gene decryption - scientific divination.
3. Ever Young BioDimension: Joint venture of CMU-AURORA, a new start-up for upgraded value.
4. EVER FORTUNE.AI: Integration of smart medicine and technology.
5. Ever Supreme Bio Technology: The first-approved biotech company to launch dendritic-cell therapy for treating all stages of cancers in Taiwan.

The world is embracing the development of artificial intelligence (AI). Therefore, CMU and CMUH are actively working to establish an AI Smart University and Hospital by developing AI, big data, 3D printing, minimally-invasive medical devices, AI-assistive devices, new drug development, and cutting-edge medicine. At the same time, CMU and CMUH assist spin-off companies in developing medical devices to promote the healthcare industry and economic development.

“China Medical University and China Medical University Hospital not only want to become ‘the pride of Taiwan’, but also strive to become an outstanding brand in the world.”

To further this goal, CMU is now building the “CMU SN Biotechnology Research Park.” Frank Gehry, Pritzker Architecture Prize Laureate, was invited to design the Medical Innovation Building, and the Pritzker Architecture Prize winner RCR Arquitectes was invited to design the sports stadium. The CMU SN Biotechnology Research Park will become a highlight of Taiwan’s AI University and also a brand new landmark for Taichung and Taiwan.

Research Breakthroughs

President Mien-Chie Hung Publishes New Target Therapy for Liver Cancer Treatment in the Prestigious Journal *Nature*

President Mien-Chie Hung’s international research team have made a breakthrough discovery: the gluconeogenic metabolic enzyme PCK1 has protein kinase activity and can be used as a new target for liver cancer treatment. The study “The gluconeogenic enzyme PCK1 phosphorylates INSIG1/2 for lipogenesis” was published in the journal *Nature* (Impact Factor 43.07).

PCK1 (phosphoenolpyruvate carboxykinase 1) is a key metabolic enzyme for gluconeogenesis in liver and kidney. Its main function is to convert OAA (oxaloacetate) into PEP (phosphoenolpyruvate). This process of converting non-carbohydrates into glucose is an important physiological mechanism for maintaining the balance of blood sugar. Previous studies have also pointed out that PCK1 is an important tumor suppressor gene, showing that PCK1 plays a crucial role in physiological balance and cancer prevention.

However, the team found that under abnormal growth stimulation, cancerous liver cells will cause the phosphorylation of PCK1 through the AKT signaling pathway. This changes the function of PCK1 and leads to the mechanism of lipogenesis, resulting in the massive production of cholesterol and fatty acids that directly facilitate cancer development. “The great significance of this research is to discover that PCK1, which should have been a tumor suppressor gene, was transformed into a carcinogen during the canceration process. This is completely different from its original function. Besides, when this kind of PCK1 phosphorylates the downstream molecule Insig1/2, GTP is used as the phosphate source rather than the common ATP. This is also very special,” said President Hung.



In clinical application, the phosphorylated PCK1 formed by cancer cells will be the most ideal therapeutic target, due to the drugs that inhibit phosphorylated PCK1 will only kill cancer cells without affecting normal cells. This is an important breakthrough for future research since there are no available drugs currently. Moreover, the team pointed out that in addition to liver cancer cells, the same PCK1 phosphorylation was found in other cancer cells, which means that this new strategy is expected to be widely used in various cancer groups and has a great clinical value.

This research pointed out a new direction for new drug development and showed that the canceration turning point of phosphorylated PCK1 itself is the best drug target. With this new finding, it is expected that the treatment for liver cancer will be strengthened and bring a breakthrough in the history of precision medicine research.

Good News for Melanoma Patients!

President Mien-Chie Hung Publishes Research Findings in the Journal *Cancer Cell*

President Mien-Chie Hung, a world famous cancer researcher, guided an international research team that published the study, “ADORA1 Inhibition Promotes Tumor Immune Evasion by Regulating the ATF3-PD-L1 Axis” in the March 16th, 2020 issue of *Cancer Cell* (Impact Factor 23.9). This research was completed with the cooperation of the Xiangya Hospital of Central South University in China. It showed an effective strategy for the immunotherapy for screening melanoma.

Melanoma is a malignant tumor caused by the abnormal proliferation of melanocytes and is the number one cause of skin tumor death. The melanoma research team first revealed that the molecular mechanisms of adenosine signaling pathway ADORA1-ATF3 axis regulated PD-L1 tumor, provided a new strategy of ADORA1 antagonist combined with PD-1 blockade for effective melanoma treatment, and identified a reliable screening method for predicting the therapeutic effect of PD-1 blockade.

CMU International Research Team Publish in the Journal *Cell*, with Taiwan's National Bird "Formosan Magpie" Honorably Selected as Cover Picture



An international research team led by CMU investigated the mystery and the evolution of birds' flight feathers from different science perspectives. Their article, "The Making of a Flight Feather: Bio-architectural Principles and Adaptation,"

was published in the November 27th, 2019 issue of *Cell*. The issue's cover photo was a Formosan Magpie, Taiwan's national bird, which showed the beauty of Taiwan to the world's academics.

CMU Center of Excellence for Integrative Stem Cell organized a cross-disciplinary research team to explore feathers from different aspects, including the biophysical characteristics of feathers and the basic molecular biology of stem cell formation. To probe into the origin of feathers' complex structure, the research team also analyze an amber fossil that was recently discovered in Myanmar. The amber preserved a delicate three-dimensional structure that hasn't been found before. CMU's research team discov-

ered that the ancient feathers possessed similar basic structure but with more primitive characteristics.

"We learned how skin turns into feathers, how feathers transform into various structures of down feathers, contour feathers, and flight feathers. Moreover, how flight feathers adjust to accommodate the living environment. It is the feathers' adaptable modular structure that makes birds successfully adapt to different environments," explained Academician Cheng-Ming Chuong.

Dr. Shih-Chieh Hung, the Director of Center of Excellence for Integrative Stem Cell, added "The structure of feathers is an inspiration to future innovative biomimetic applications. The invention of composites may help in building light but firm unmanned aerial vehicle (UAVs), durable and elastic wind turbine, better medical implants, and prosthetic devices."

The CMU research team focus on both basics and applications in the research. Furthermore, they explored the principle of biomaterial structures inspired by nature, and the application in the design of biomimetic materials. The team will also expand their research in the area of molecular signaling, in order to investigate how the stem cells in hair follicles are guided to construct complex biological structures.

Professor Kuan-Pin Su Publishes Research in the Journal *Sleep Medicine Review* on a New Discovery of "Nutrition Treatment in Delirium Prevention"

CMU Professor Kuan-Pin Su has been dedicated to the research on the prevention of delirium. Disruption of the sleep-wake cycle is a risk factor of delirium. Therefore, based on the analysis and clinical research of melatonin and its receptor agonist ramelteon, Professor Su's international research team found that "nutritional supplements and related medicine for melatonin have a significant effect on prevention of delirium for severe patients." This article, "Melatonergic Agents in the Prevention of Delirium: A Network Meta-Analysis of Randomized Controlled Trials," was published in the April 2020 issue of *Sleep Medicine Review*, the top journal in the field of sleep medicine (Impact Factor 10.5).

Circadian rhythms are important indicators of a human being's physical and mental health. Normal circadian rhythms can maintain one's memory, metabolic, immune, cardiovascular, and skeletal muscle functions. The Mind-Body Interface Laboratory (MBI-lab) led by Professor Su has already published fruitful findings on related topics. In the latest research, Professor Su's team reported that the nutritional supplements of melatonin and related drugs (such as ramelteon) under appropriate uses can effectively prevent delirium. If this research can be validated by a larger clinical trial in the future, it will surely bring a great clinical value to the patients and clinicians. In addition to providing a new treatment and future guideline for treating delirium, this research is expected to become a new direction for the treatment and prevention of psychiatric disorders.



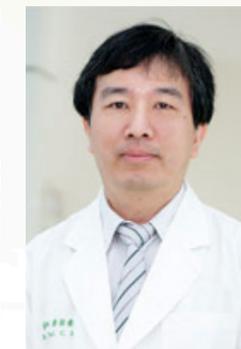
Chair Professor Chung Y. Hsu and Professor Chon-Haw Tsai's Team Publish in *The New England Journal of Medicine* on Clinical Research of Thrombolysis for Acute Ischemic Stroke

The article, "Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke," is an international cooperation project funded by Australian National Health and Medical Research Council. It aimed to find out the efficacy and safety outcomes of patients receiving intravenous alteplase or placebo between 4.5 and 9.0 hours after the onset of stroke. Nine hospitals in Taiwan participated in the study, under the leadership of CMU Chair Professor Chung Y. Hsu and Professor Chon-Haw Tsai.

The result showed that after 90 days of treatment, the alteplase group significantly surpassed the placebo group in the recovery of the neurological function. In addition, the safety of alteplase treatment did not differ significantly from the traditional group. The research finding was published in the May 2019 issue of the *The New England Journal of Medicine* (Impact Factor 70). It will surely bring an important contribution to stroke treatment in the future.



Prof. Chung Y. Hsu



Prof. Chon-Haw Tsai



Outstanding Awards

Superintendent Rue-Mo Lin of CMU Tainan Municipal An-Nan Hospital Receives Medical Contribution Award

Dr. Rue-Mo Lin has dedicated himself to cultivating medical talents in the field of spine surgery. He led the first Taiwan Medical Team to Vietnam to instruct the local surgeons about scoliosis surgery in 2004, which promotes Taiwan's high quality medical service to the world. Dr. Lin's effort in international medical exchanges and personnel training has broadened the international visibility of Taiwan's soft power in spine surgery.

Vice President Fuu-Jen Tsai of CMU Receives 2019 Taiwan Medical Model Award

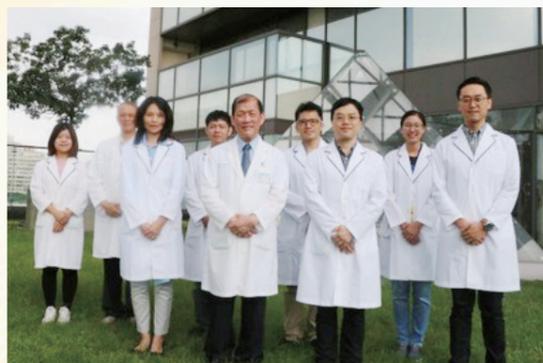
Dr. Tsai established Taiwan's first Rare Diseases Drug Distribution Center and Taiwan Rare Diseases Organization Database, and has made significant contributions in the diagnosis and treatment of Children's Kawasaki disease in Taiwan.



Vice President Cheng-Chieh Lin of CMU Receives 2019 Taiwan Medical Contribution Award

Dr. Lin actively worked towards providing medical services for both the rural areas and the elderly. In addition, he had shown outstanding leadership by promoting the transformation of Taiwan's medical education system. Dr. Lin has also worked with the medical school/hospital accreditation of Taiwan Medical Accreditation Council (TMAC).

CMU Awardees of the 16th National Innovation Award Superintendent Der-Yang Cho, China Medical University Hospital



Superintendent Der-Yang Cho led the CMUH Cell Therapy Center and made the breakthrough finding “Multiple carcinoma targetable CAR for immune cell therapy.” The team discovered that the immune checkpoint protein HLA-G can be used for targeting multiple solid tumors. In addition, the chimeric antigen receptor (CAR) immune cells designed with this protein also demonstrated the ability to kill solid tumors.

Through screening and analyzing large amount of clinical tissue samples, the team found an immune checkpoint protein HLA-G that has a high expression in various solid tumors and has the function of inhibiting immune cell activity.

Dean Lih-Jyh Fuh, CMU College of Dentistry

Dean Fuh led a cross-university research and development team and launched a newly developed dental image instrument “The Novel Application to Digital Dental X-Ray by Intraoral Tomosynthesis System.”

By using this new system, dentists can obtain three-dimensional images just by a single limited-angle scan. After reconstructing the images from different angles, the system can provide voxels with anatomical structure data. With a special software, the visualization of different cutting planes can be manipulated and be applied to clinical technologies for dental implant, root canal therapy, and dental reconstruction.



3D Printing Medical Center, China Medical University and Asia University

The 3D Printing Medical Center of China Medical University and Asia University received the award for the project on “Innovative Cell Blocks for 3D Artificial Dermis Development.” The center manufactures a new kind of artificial dermis with 3D cell blocks combining with a 3D collagen base. This artificial dermis possesses the physical properties of natural skin with good biocompatibility. In addition, the cell blocks can secrete extracellular matrix and growth factors to provide a growth environment for skin tissue repair and to accelerate the reconstruction of skin tissue.

CMU’s Spin-off Company “EVER FORTUNE.AI”

The research and development team led by Dr. Tzung-Chi Huang, CEO of EVER FORTUNE.AI, received the National Innovation Award for their innovative system “Medical AI for Diagnosis in Healthcare.” This intelligent medical assisted diagnosis system can serve as a model training material in various fields such as computed radiography, computed tomography, ultrasound, and magnetic resonance imaging. Moreover, the system can assist physicians in clinical diagnosis throughout all parts of the body.



CMU’s Epidemic Prevention for COVID-19

CMU Alumnus Dr. Chunhsin Lee Invented a Unique Patent-Certified “Chinese Medicine Face Mask”

COVID-19 has made face masks popular products. Dr. Chunhsin Lee, an alumnus of CMU and a Chinese medicine expert, has devoted himself to inventing a Chinese Medicine Face Mask that has an innovative way to block infectious diseases while also providing therapy to the wearer. This invention has obtained three technical patents and its innovative design has made it stand out in the market.

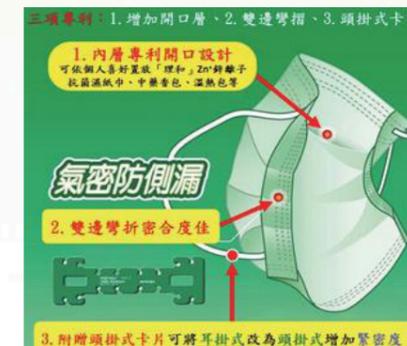
The three patents are:

1. Penetration rate: This innovative mask consists of four layers (most medical masks consist of only three layers). The extra layer is an open layer that can hold herbal sachets or

tea/coffee scented bags and provide an innovative way of therapy.

2. Fitness for the face: Common medical masks cannot be completely sealed on the left and right sides of the face, which is likely to cause the inhalation of PM2.5 particles. This mask adds protective layers on the left and right sides of the mask to make it fit the wearer’s face, which makes the mask more effective in preventing viruses along with keeping the wearer safe from air pollution.

3. Tightness: The human face is not completely flat, so the common ear-hook type masks are not well fit for



the face. This mask is attached with cardboard, which switches it from an ear-hooked to head-suspended mask. This will give the mask a better fit to the mask and make it less air resistant.

Protect the Health of the Community!

CMU Students Help Pharmacies with Mask Distribution



An early preventive measure against COVID-19 in Taiwan was a face mask rationing system, which limited the number of face masks people could buy. This program was critical in ensuring that everyone in Taiwan had access to face masks, but it meant much more work for pharmacies selling them. Forty CMU students from the School of Pharmacy volunteered their time to help local pharmacies in Taichung with the added workload. Among the 40 students were four international students. One of them stated that “helping Taiwan during this difficult time is a social responsibility that students of School of Pharmacy are willing to take.”

National Quemoy University Sends Gifts to Thank China Medical University

On February 11th, 2020, in response to COVID-19, Taiwan imposed an entry ban for Hong Kong and Macau residents. The night before the ban, two Hong Kong students flew back to Taiwan. They are friends, but study at different universities. One studies at Kinmen’s National Quemoy University (NQU), with the other studying at CMU. Due to the limited transportation options that night, the NQU student was unable to complete the journey to the offshore island of Kinmen. As a result, the CMU student invited her to stay in her apartment. They both arrived in Taichung on a special CMU shuttle bus. After returning to Taichung, they followed the regulation of home quarantine for 14 days.

CMU assisted home quarantine students by providing personal hygiene products and food delivery service. In order to express its gratitude, NQU sent a pair of Kinmen Wind Lions along with several Kinmen souvenirs to CMU.



“In the period of epidemic prevention, we should help each other and work in unity,” said CMU President Mien-Chie Hung.