CMU GLOBAL CONNECTION

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International Collaborations and Joint Symposium

Strengthen International Collaborative Research: The 6th NUS-CMU Joint Symposium

Since establishing collaboration in 2016, CMU and NUS have continued to carry out frequent academic exchanges. Professors from the both universities make research cooperation, implement joint research projects, co-supervise PhD students and participate in joint symposiums.

The National University of Singapore hosted the 6th NUS-CMU Joint Symposium on November 26-27, 2024. In the symposium, 7 scholars from CMU and 12 scholars from NUS gave special lectures, focusing on topics including tumor immunity, cancer epigenetics, traditional Chinese medicine for cancer treatment, and the protective mechanism of electroacupuncture on the nervous system. Academician Mien-Chie Hung, the President of CMU, served as the keynote speaker and delivered a speech titled “Marker-Guided Effective Therapy (MGET).” He shared the latest research results of cancer marker-guided therapy, emphasized personalized treatment strategies based on marker guidance, and demonstrated the application of a new generation of intracellular messaging imaging technology.

During the two-day meeting, scholars from both universities had lively discussions and proposed more than 10 potential collaborative projects, covering the topics of tumor microenvironment regulation, innovative drug delivery technology, and clinical application and new mechanism research of traditional Chinese medicine and acupuncture therapy. With the fruitful discussion results, the research teams of CMU and NUS hope to apply for the seed funding and, furthermore, apply for the international collaboration project of Taiwan and Singapore. In the future, we can expect that CMU and NUS will continue to perform highly influential, cutting-edge research to benefit the public.

2024 CMU-MU Joint Symposium on Traditional Medicine and AI Application

China Medical University and Mahidol University (Thailand) co-organized the 2024 CMU-MU Joint Symposium on Traditional Medicine and AI Application. This symposium focused on the application of AI in traditional Chinese and traditional Thai medicines, the continued importance of traditional medicines in modern medical care, and the huge potential of AI technology for the development of medicine.

Experts from both universities shared their experience related to AI technology. Vice President Lu-Hai Wang introduced the CMU Center of Excellence for Chinese Medicine and their efforts in promoting the modernization and internationalization of traditional Chinese medicine, especially the progress of applying AI technology to the research and practice of traditional Chinese medicine. Dean Hung-Rong Yen, College of Chinese Medicine, shared how advanced technology plays an important role in the diagnosis, treatment, education, and research in Chinese medicine. Dr. Wan-Yu Lai, Director of CMUH Division of Chinese Pediatrics Medicine, shared about the innovative structured teaching model used in traditional Chinese medicine pediatric massage, demonstrating the enhanced teaching results of integrating AI technology to traditional techniques.

Prof. Pravit Akarasereenont from Mahidol University gave a speech detailing what Thai medicine is and further explored ways AI technology could be used to customize personal health plans, improve curative effects and prevent diseases.

A special addition to the symposium was the workshop on “Treating Low Back Pain in Thai Traditional Medicine,” hosted by Assistant Professor Supakij Suwannatrai and Dr. Ketmanee Jongjiamdee. They introduced the highly practical Thai traditional medical technology and discussed its application value in modern clinical practice.

Through academic exchanges and cooperation between CMU and MU, we not only understand the modern development trend of traditional medicine in Taiwan and Thailand, but also see the prospects of applying AI in global health management, bringing more breakthroughs to future medical technology innovation.

CMU and Kyoto University Jointly Established the 13th Global Research and Development Center

On November 19, China Medical University and Kyoto University signed an MOU agreement and held the opening ceremony of the Kyoto University Global Research and Development Center. This is the 13th On-site Lab (OSL) established by Kyoto University in the world, aiming to strengthen the cooperation between the two universities in the fields of cancer research, translational medicine, stem cell regenerative medicine and advanced drug development and to bring new energy to the medical development worldwide.
The Global Research and Development Center will focus on three major areas of research:

1. Cancer Biology: To promote the development of precision cancer treatment.
2. Regenerative Medicine: To promote the development of cell, gene and exosome therapies.
3. Advanced Drug Development: To develop advanced drugs for which there is no current drug treatment.

The 2nd CMU-KU Joint Symposium

After the opening ceremony of the Global Research and Development Center, the two universities held the 2nd CMU-KU Joint Symposium. Seven scholars from Kyoto University and six from China Medical University shared their research results in the fields of data science and smart medical care, immunity and cancer immunotherapy, regenerative medicine, and RNA targeting and exosome therapy.

The symposium not only showcased the latest achievements of CMU and KU in cutting-edge medicine but also facilitated several new cooperation projects. The cooperation between CMU and KU has built communication platform for the biomedical communities in Taiwan and Japan and expanded the global biomedical academic network. With the establishment of the 13th Global Research and Development Center, CMU and KU look forward to making more breakthroughs in the fields of cancer and regenerative medicine, jointly promoting global medical progress, and becoming a milestone in the development of cancer regenerative medicine.

International Forums held by China Medical University and Healthcare System

International Forum of Extracellular Vesicles Technology and Novel Therapeutics

China Medical University and Healthcare System held the International Forum of Extracellular Vesicles Technology and Novel Therapeutics on November 2, 2024. This forum aims to promote Taiwan's exosome-related research, to link with international standards, and to open new horizons for the application of exosome technology in the biomedical field. Professor Randy Wayne Schekman, winner of the 2013 Nobel Prize in Physiology or Medicine, was invited as the keynote speaker. Top scholars and industry leaders in the field of exosomes discussed the latest breakthroughs and applications of exosomes, also known as extracellular vesicles, in basic research, innovative technologies, and product development.

Professor Schekman elaborated on exosomes as a key bridge for intercellular factor transmission, the latest research progress in improving the efficiency of exosome delivery through quantitative scientific methods and also demonstrated the potential of exosome technology to achieve therapeutic effects.

"Extracellular vesicles play a key role in biological processes such as aging, inflammation, disease progression, and intercellular signaling. In the future, exosome technology may become the core of the development of biological agents, bringing a new chapter in promoting human health." said Chairman Chang-Hai Tsai.

"The exosome platform will lead a new direction in the treatment of cancer and neurodegenerative diseases, focusing on developing drugs that can reduce drug dosage and side effects. However, its large-scale manufacturing technology still needs breakthrough. We hope that more researchers will join us to create a new era of biotechnology together." said Superintendent Der-Yang Cho.

2024 International Conference on Advanced Biomedical Sciences (ICABS)

China Medical University held the 4th International Conference on Advanced Biomedical Sciences (ICABS) in October 2024. Top scholars from the world were invited to share their latest research, including Dr. Joseph Schlessinger (National Academy of Sciences), Dr. Jenny P. Y. Ting (National Academy of Sciences), Dr. Zhijian "James" Chen (National Academy of Sciences), Dr. Ashok Venkitaraman (Singapore National Academy of Science), and Dr. Hsing-Jien Kung (Academia Sinica, Taiwan). The conference provided an excellent platform for students and young scientists to absorb new knowledge and keep up with the world and also enhanced the status of Taiwan's biomedical research and technology in the international community.

The conference focused on the most cutting-edge cancer research, including biology, cancer immunity, target identification and treatment, immune biochemical pathways, cancer metabolism, and cancer translation research. Moreover, a special session was held to provide an opportunity for the participants to interact with the editors-in-chief and senior editors of Science, Nature, Cancer Cell, and Cell Reports Medicine. This is very helpful for increasing the number of publications in high-impact journals. The conference also highlighted the new National Science Council's (Taiwan) major national cancer research plan, the Taiwan Cancer Dream Team.

The International Conference on Advanced Biomedical Sciences was founded by Academician Mien-Chie Hung, President of CMU. It has been held every year since 2021 and has become an important conference in Taiwan's biomedical field. We look forward to achieving major scientific breakthroughs through exchanges and cooperation between top scientists worldwide and working to the goal of having Taiwan's research results in biomedical science globally known.

Outstanding Awards

2024 Future Technology Award

Stem Cell-Nanoparticle-System for Neutron Capture Therapy of Malignant Glioblastoma Multiforme

New breakthrough in cell therapy! A collaborative research team led by Professor Long-Bin Jeng of China Medical University Hospital has successfully developed a cutting-edge cell therapy platform that combines stem cells, nanotechnology, and neutron capture therapy that can accurately attack the most malignant glioblastoma multiforme.

The research team used nano-armor technology to wrap stem cells in multifunctional nanocarriers to form a stem cell-nanoparticle system (SNS). The advantages of this system include: (1) Magnetic iron oxide allows stem cells to accurately accumulate in the brain under the guidance of a magnetic field. (2) The tumor homing properties of stem cells ensure that drugs can be targeted to brain tumors for a second time. (3) The fucose component provides anti-inflammatory and neuroprotective effects that can reduce the side effects of treatment.

This platform technology breaks the limitations of traditional cell therapy in the treatment of brain cancer and can precisely attack tumor cells. Compared with traditional neutron capture therapy, SNS shows a higher tumor-to-blood ratio, better efficacy, lower dosage, more convenient administration, and lower side effects. In addition, this platform technology can not only be used for stem cells but can also integrate immune T cells or dendritic cells for immunotherapy.

Currently, the research team has developed continuous nanoparticle manufacturing technology to ensure product stability to prepare for mass production and commercialization in the future. It is expected that this platform, combined with big data, will accelerate the development of nanoengineered cell biologics for different diseases and bring new hope for patients.

2024 Future Technology Award

35d Small Molecule Drug that can Overcome Drug-Resistant Lung Cancer

The oncology and pharmaceutical chemistry research team of China Medical University successfully developed a 35d small molecule drug that can overcome drug-resistant lung cancer. This breakthrough therapy, "Curcumin derivative 35d for the treatment of EGFR mutation TKI-resistant lung cancer," was awarded the 2024 Future Technology Award by the National Science Council and was selected as this year's Highlight Technology.

Lung cancer is one of the deadliest cancers in the world, especially in Asia, where about 50% of non-small cell lung cancer patients have EGFR (epidermal growth factor receptor) gene mutations. Although EGFR kinase activity inhibitors are effective in early treatment, most patients relapse within 1 to 2 years due to drug resistance. Therefore, they face the challenge of having no effective treatment, and this affects hundreds of thousands of patients globally every year.

Assistant Professor Pei-Chih Lee, the project leader of this research, explained that the development of 35d drugs is based on in-depth research on EGFR. The team used shRNA technology to reduce EGFR protein expression and found that it can effectively inhibit the growth of more than 20 types of lung cancer cells that have become resistant to EGFR kinase activity inhibitors. This discovery confirms that reducing EGFR protein expression is an effective strategy for this drug-resistant lung cancer.

In addition to being recognized by the 2024 Future Technology Award, this technological advancement won the Taipei Biotechnology Award in 2023. Currently, the technology of 35d drug has been licensed to Launxp Biomedical Co., Ltd., and it is expected to provide a new and effective treatment option for patients with recurrent lung cancer and benefit more patients in the future.

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Research Breakthroughs

Oral Administration of Ketamine is Effective in Treating Treatment-Resistant Depression! CMU Professor Hsien-Yuan Lane and Research Team Published Research Results in *Nature Medicine*

Professor Hsien-Yuan Lane, the Director of the Institute of Biomedical Sciences at CMU, is an internationally renowned psychiatrist and psychopharmacologist. Based on medical evidence that ketamine has an improving effect on treatment-resistant depression (TRD), Professor Lane and his research team participated in a multinational phase 2 clinical trial. They found that with oral administration in the form of sustained-release tablets, the safety and tolerability of ketamine may be improved. Their study “Extended-release ketamine tablets for treatment-resistant depression: a randomized placebo-controlled phase 2 trial” was published in the journal Nature Medicine and has received great attention from the medical community.

Over the past two decades, increasing medical evidence has shown that ketamine has a rapid antidepressant effect in patients with TRD. However, most published studies have used racemic ketamine off-label and usually given by intravenous injection. The phase 2 clinical trial in which Professor Lane’s team participated brought together 20 psychiatric departments from New Zealand, Australia, Singapore, and Taiwan to screen 329 adult patients with TRD between 2019 and 2021, of whom 231 met the criteria for this clinical trial. They first received open-label ketamine R-107 extended-release tablets 120 mg per day for 5 days and were assessed on day 8. Responders (MADRS score ≤ 12 and reduction ≥ 50%) were randomized in equal proportions to receive a double-blind dose of extended-release ketamine (30, 60, 120, or 180 mg) or a placebo, twice weekly for a further 12 weeks. Non-responders on day 8 exited the study.

The results showed that the 180 mg group had better efficacy and was well tolerated compared with the placebo group. During the randomized phase of the study, most patient dosing occurred at home. Therefore, it can be concluded that in this phase 2 clinical trial, ketamine extended-release tablets were effective, safe, and well tolerated in the treatment of patients with TRD.

CMU Professor Chin-Chi Kuo and Research Team Published Research Results in *Nature Communications* for Their Study in Causes and Prevention of Chronic Kidney Diseases in Taiwan

“Discovery and prioritization of genetic determinants of kidney function in 297,355 individuals from Taiwan and Japan” is a study completed by the research team led by Professor Chin-Chi Kuo. It was published in the top international journal Nature Communications and received widespread attention in the medical community.

The study was the first large-scale study of kidney disease gene variation in East Asians. It not only revealed that East Asians may be born with relatively insufficient kidney function development and maintenance but also partially explains why Taiwan, for many years, has had the highest rate of end-stage renal disease in the world. It is expected that in the future the congenital susceptibility to renal dysfunction will be screened out through genetic testing to identify patients at high risk of chronic kidney disease who can take “advanced-preventive” measures, such as early and more stringent intervention in blood pressure and blood sugar screening and treatment, as well as strengthen the control over environmental exposure factors that affect renal function.

Taiwan has more than 90,000 hemodialysis patients, ranking the highest in the world, and most patients have no obvious symptoms of early kidney disease. The research team used digital medical information and AI as the basis, integrating the genetic data of the human biobanks in Japan and Taiwan. The team worked with two China Medical University Hospital centers: the Big Data Center’s iHi Platform and the Center for Precision Medicine’s massive gene data. The research involved a large-scale analysis on the genetic variations of kidney disease in East Asian populations. This study filled the gap of Asian population representativeness in global kidney disease research. Several new genes closely related to renal function were successfully identified and verified, including the F12 and ABCG2 genes.

The next step for the research will be to construct and evaluate whether the “advanced-prevention” strategy can effectively prevent and treat chronic kidney disease, hoping to reduce Taiwan’s long-term burden of kidney disease care.

The Mechanism of Regulating Protein Lipoylation is Expected to Become a New Strategy for Cancer Targeted Clinical Therapy! CMU Professor Ming Tan Published Research Findings in *Trends in Biochemical Sciences*

Diabetes and cancer are both among the top ten causes of death in Taiwan and are classified as abnormal cell metabolism diseases. Therefore, cell metabolism diseases have always been a key topic of research in the international biomedical community. However, how to effectively control the disease and overcome drug resistance is a difficult issue that clinical cancer medicine is facing.

Currently, there are only five confirmed lipoic acid proteins in the human body, and all of them are important enzyme proteins that play a key role in regulating metabolism in the mitochondria, the power plant of the human body. CMU Professor Ming Tan’s research team collaborated with the Cancer Center of Brown University, and through data analysis, they found that the expression of genes related to the protein lipoylation pathway was significantly different between cancer patients and non-cancer patients, indicating that the post-translational modification of the protein is an important potential indicator of cancerization. Studies have shown that regulating protein lipoylation and the closely related copper ion-induced cell death is expected to become a new strategy for cancer-targeted clinical therapy. Their

latest study, “Protein lipoylation: mitochondria, cuproptosis, and beyond,” published in the journal Trends in Biochemical Science, discussed the relationship between protein lipoylation and metabolic diseases and proposed many research and clinical treatment strategies that are worthy of further exploration and clinical application.

In 2022, Dr. Peter Tsvetkov and his research team from Harvard University had proposed a newly discovered form of programmed cell death: cell copper apoptosis. Its activation mechanism mainly involves excessive copper ions and protein lipoylation. Many review papers have discussed the effects of copper ions on pathology, focusing on the many clinical medical data analyses pointing out that high copper ion concentrations lead to cancer deterioration. However, there are only a few reviews and analyses on protein lipoylation.

Therefore, the collaborative team of CMU and Brown University conducted further analysis on the mechanism and source of protein lipoic acidification, as well as the potential of using this mechanism to design research and medical strategies for metabolic diseases. Their study on abnormal metal ion metabolism and its association with cancer and other cellular metabolic diseases provides new development directions and potential strategies in clinical treatment.

The research team adopted a variety of screening strategies, including natural compounds and synthetic derivatives, and successfully developed the innovative small molecule drug 35d. Unlike traditional EGFR inhibitors that can only inhibit the EGFR kinase activity of cancer cells, the 35d drug can activate the hsp70 signaling pathway, promote EGFR protein degradation, and significantly reduce the expression of mutant EGFR protein in cancer cells, thereby inducing the death of drug-resistant cancer cells. In multiple preclinical tumor models, the 35d drug showed significant therapeutic effects.