CMU GLOBAL CONNECTION

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China Medical University
Newsletter Issue #1

About China Medical University

Established in 1958, China Medical University (CMU) in Taichung, Taiwan, has since developed into one of the world's premiere medical research universities with 9 colleges: Medicine, Chinese Medicine, Pharmacy, Biopharmaceutical and Food Sciences, Public Health, Health Care, Dentistry, Humanities and Technology, along with Biomedical Engineering. Its Joint Commission International (JCI)-accredited hospitals have a total of over 5,800 beds, and it is the second largest healthcare system nationwide providing superb service in both western and Chinese medicine.

CMU trains both western medicine doctors and Chinese medicine doctors and implements the best integration of western and Chinese medicine at China Medical University Hospital providing outstanding medical service to cancer patients. As a leader in several research fields with a culture of collaboration and innovation, CMU has made important breakthroughs in cancer treatments such as inventing combined target therapy and immune checkpoint therapy to overcome difficult malignancies, lengthening the survival of glioblastoma patients, discovering ANK-199, a promising anticancer drug that treats head and neck cancer, and identifying the receptor protein IL-17RB that is strongly associated with pancreatic cancer. The Center of Excellence for Chinese Herbal Medicine was awarded with a Top-Notch Center Grant from the Ministry of Education and conducts many lines of clinical studies evaluating the effect of Chinese herbal medicine. The Center of Excellence for New Drug Development was awarded with a Top-Notch Center Grant and aims to develop novel drugs.

International collaborative partnerships with prestigious institutions such as Stanford University, the M.D. Anderson Cancer Center, University of California, Irvine (UCI), National University of Singapore, Nanyang Technology University, University of Tokyo and Seoul National University

have been firmly established. Additionally, over 80 international healthcare companies and venture capitalists are assisting the university with its knowledge transfer mission. Thus far, over 60 new drugs have emerged from CMU's research laboratories, as well as 9 new spin-off companies.

CMU Glory Profiles

2019 Times Higher Education (THE)
Asia University Rankings: 60
(3rd in Taiwan, 1st among private universities)
Best "Golden Age" University: 72
(1st in Taiwan)

2018 Academic Ranking of World Universities (ARWU): 244

Receipient of the "2019 Top 20 University Excellence Award"
by Cheers Magazine

2nd Best Private University on Taiwan's Best University Ranking
by Global Views Monthly

Research Breakthroughs

Good News for Target Therapy Treatment: President Mien-Chie Hung's Research Team Published on Cancer Cell Journal:

"Removal of N-linked glycosylation enhances PD-L1 detection and predicts anti-PD-1/PD-L1 therapeutic efficacy"

The mystery of why the protein PD-L1 cannot be detected in cancer patients has been solved! China Medical University (CMU) President Mien-Chie Hung and his international research team has developed a new strategy that makes the target therapy more precise and can be widely used in treating various cancers.

The study "Removal of N-linked glycosylation enhances PD-L1 detection and predicts anti-PD-1/PD-L1 therapeutic efficacy" was published in Cancer Cell on July 19th, 2019. It received high attention and praise from the international medical community.

In the current target therapy, anti-PD-L1/PD-1 immunotherapy has become a revolutionary principle. It brings significant therapeutic effect to 20-40% of patients on average. However, a previous unsolved phenomenon has long existed. Theoretically, only PD-L1-positive patients are responsive to "anti-PD-L1/PD-1" treatment. But 10-20% PD-L1-negative patients also respond to anti-PD-L1/PD-1 treatment. This has been a clinical mystery.

It turns out the current methods for detecting PD-L1 are not perfect, so the expression levels of PD-L1 in patients' specimen is not an ideal biomarker to effectively determine whether patients are suitable for the accurate anti-PD-L1/PD-1 immunotherapy. Since that PD-L1 is a highly glycosylated protein, the research team therefore hypothesized that in the tissue samples of a particular patient group exist PD-L1 proteins coated with specific glycan structure, thus hindering the binding of anti-PD-L1 antibodies (mAb clone 28-8) in clinical detection of PD-L1 and resulting in false negative outcomes. Therefore, these patients do respond positively to anti-PD-1/PD-L1 treatment but lost the chance to receive the immunotherapy due to false negative detection results.

President Hung's team has thus developed a new therapeutic strategy, which is to apply specific enzymes to remove the glycosylation on the PD-L1 protein, so that it can be recognized by the PD-L1 antibody. Using tissue microarrays, the team proved this new strategy effective in detecting approximately 16% of the total patient population. These patients were PD-L1-positive and benefited from anti-PD-1/PD-L1 treatment, while with traditional method they were diagnosed with PD-L1-negative.

This newly developed strategy for cancer immunotherapy can identify PD-L1-positive patients more accurately and further help them benefit from the immunotherapy. Most of all, this new strategy may be widely used in various types of cancer, which brings great clinical values.

Breakthrough for Cancer Immunotherapy!

President Mien-Chie Hung's Research Team Published on Journal of Clinical Investigation:

"IL-6/JAK1 pathway drives PD-L1 Y112 phosphorylation to promote cancer immune evasion"

China Medical University (CMU) President Mien-Chie Hung's research team cooperated with the MD Anderson Cancer Center in research that found the combined treatment of IL-6 antibodies and anti-T-cell immunoglobulin mucin-3 (anti-Tim-3) can attenuate the development of drug resistance of cancer cells and enhance the efficacy of immunotherapy. This will greatly benefit cancer patients and is a significant breakthrough in immunotherapy.

The research finding "IL-6/JAK1 pathway drives PD-L1 Y112 phosphorylation to promote cancer immune evasion" was published on the Journal of Clinical Investigation on July 18th, 2019. It received high attention and recognition from the international medical community and promoted Taiwan's cancer research reputation.

Immunotherapy has been regarded as a new hope for cancer treatments. The US Food and Drug Administration (FDA) has approved a number of clinical therapeutic antibodies. However, there are still some hidden cancer cells that can survive from the attack of immune cells. "PD-L1 is an immunological checkpoint inhibitor, and its binding with the receptors on T cells can activates common suppressor signals. The function of cytotoxic T cells will be suppressed so that cancer cells can escape from the immune surveillance. Therefore, blocking PD-L1 or PD-1 has shown encouraging results in cancer treatments." said President Hung.

The research team also found that the glycosylation in cancer cells have the potential to become an effective biomarker in the therapy and help to enhance the treatment efficacy.

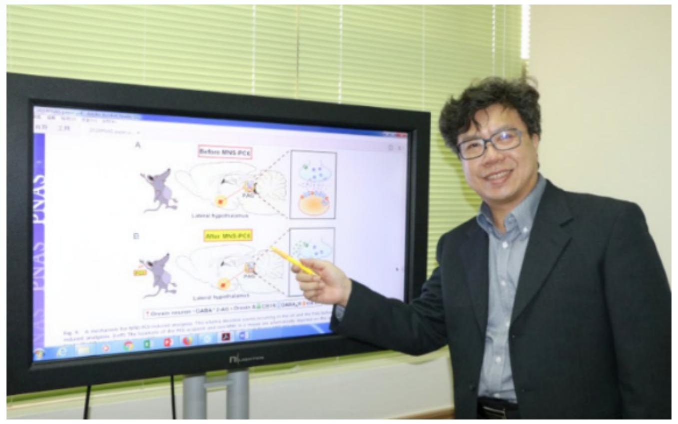
Glycosylation of immunoreceptors and ligands can modulate the activation of immune signaling and immune surveillance. PD-L1 is a highly glycosylated protein and its glycosylation can enhance immunosuppression, which leads to the drug resistance of the immune checkpoint inhibition. However, it is unclear how the carcinogenic signaling regulates PD-L1 glycosylation to induce immunosuppression. In this research, President Hung's team discovered that Janus kinase activated by IL-6 interleukin phosphorylates PD-L1, and then attracts N- Glycosyltransferases STT3A to catalyze PD-L1 glycosylation and maintain the stability of PD-L1.

In animal models, the combination of IL-6 antibodies andanti-Tim-3 induces and enhances the tumor cytotoxicity of T cells. A positive correlation between the expression of IL-6 and PD-L1 was also observed in the liver tumor tissues.

This study not only identified the mechanisms underlying the regulation of PD-L1 glycosylation, but also illustrated the combination of IL-6 antibodies and anti-Tim-3 to be an effective marker-guided therapeutic strategy. This is an exciting news for patients who still suffer from poor cancer treatment outcomes.

New Method for Pain Relief in Acupuncture Discovered by Professor Yi-Hung Chen and NTU Research Team

Professor Yi-Hung Chen of CMU Graduate Institute of Acupuncture cooperated with Professor Lih-Chu Chiou's research team from the NTU Graduate Institute of Pharmacology. They discovered a new method for pain relief in acupuncture. The research "Median nerve stimulation induces analgesia via orexin initiated endocannabinoid disinhibition in the periaqueductal gray" was published in *Proceedings of the National Academy of Sciences of the United States of America* (PNAS) on November 6th, 2018. It provided a new strategy for pain treatment and received high attention by international scholars and media.



This research found that after electroacupuncturing the inner pass (an acupuncture point), the stimulation of the median nerve will cause the hypothalamic neurons to release a neuropeptide "orexin" to the pain control region at the midbrain. Moreover, the simulation will promote endogenous endocannabinoid release, thus reducing the activity of inhibitory neuron. In the end, it leads to analgesic effects, and this analgesic mechanism is not related to endorphins.

Professor Chen said, "This research clarified the neurophysiological changes of pain relief in acupuncture, which will make traditional therapy more acceptable to the public and benefit more patients. It also provides a new theoretical basis for the painkiller development in the future." The teams from Professor Chen and Professor Chiou have been working together since 2012. The research work took 6 years to complete.

Professor Chen is currently the Associate Dean of thr CMU School of Chinese Medicine and the Secretary General of the Neuroscience Society of Taiwan. CMU's Chinese medicine research focuses on exploring Chinese medicine through modern medical technology, and applying the evidence of modern medicine to illustrate the efficacy and principles of Chinese.

Professor Wen-Hwa Lee: The Key Cause of Pancreatic Cancer is Abnormal Metabolism of Glucose

Wen-Hwa Lee, an academician of Academia Sinica and a Chair Professor of China Medical University, made a breakthrough with the research team at CMU showing that sugar is a risk factor for pancreatic cancer. Avoiding taking high sugar diet can protect the pancreas from the damage caused by abnormal metabolism and reduce the risk of pancreatic cancer. This research was published in the high impact journal "*Cell Metabolism*" on March 7, 2019.

Chair Professor Lee said, "Pancreatic cancer is one of the devastating diseases. The symptoms of pancreatic cancer are not obvious in the early stage. Usually, above 80% of the patients are diagnosed with pancreatic cancer at the final stage, in which only 20% are able to be removed by surgery. Moreover, nearly 80% of the patients that go through surgery will suffer from relapse or metastasis of the cancer. Therefore, it is crucial to understand the pathophysiologic mechanism of pancreatic cancer and furthermore develop an effective target drug. Prevention is the best cure."

Previous studies have known that pancreatic cancer is associated with abnormal metabolism of glucose, however, the cause-effect relation is unclear. The biggest contribution of this research is to demonstrate that abnormal metabolism of glucose is the "main cause" of pancreatic cancer.

In addition, the team also investigated the relationship between the high sugar diet and the development of other organ cells into cancer. They provided long-term high sugar food to guinea pigs and examined different organs of these animals including the pancreas, large intestine, small intestine, liver, lung, and kidney. The results showed that only the pancreatic tissue has a significant genomic damage and KRAS gene mutation.

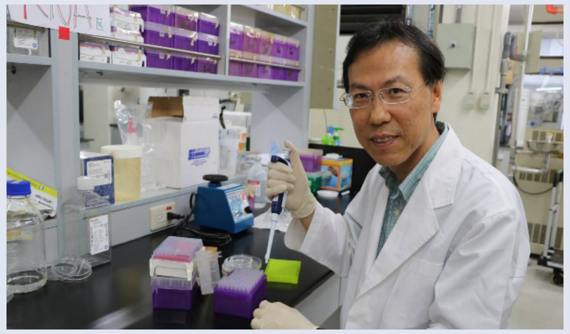
Chair Professor Lee's team published research in 2015 showing that IL-17RB antibody can attenuate the metastasis of the pancreatic cancer. This research further provides a more complete statement of the pathogenesis mechanism leading to pancreatic cancer.

CMU GLOBAL CONNECTION

Outstanding Awards
Received by CMU Faculty Members

"2018 Future Technology Award"
Ministry of Science and Technology

Professor Chow-Feng Chiang's research team
"Establishment of high performance liquid chromatography (HPLC) and QuEChERS methods for rapid determination of 15 + 1 EU priority polycyclic aromatic hydrocarbons (PAHs) in foodstuffs"



Professor Su-Hang Zhuo's research team
Development of the world's first nucleic acid interference drug which can prevent the deterioration of myopia

"The 15th National Innovation Award"

3D Printing Medical Center
Research on "3D cell spheres with the printable neural conduit for innovative medical device"

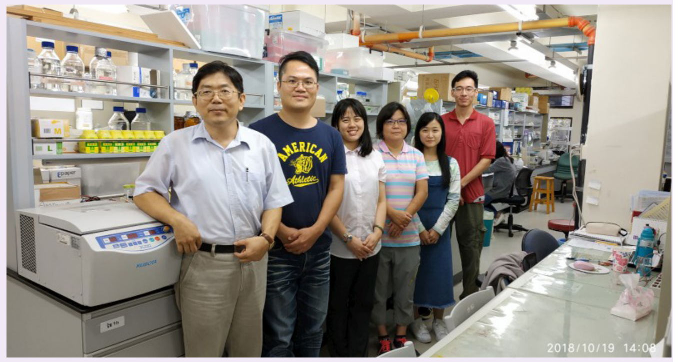
CMU's Spin-off Company"Ever Young BioDimension"
Customized 3D Medical Services

Professor Chia-Hung Hsieh's Team
Development of therapetic drugs to treat opioid addiction

Outstanding Research Award
Ministry of Science and Technology

2019 Award :
Professor Kuan-Pin Su

For his dedication to leading nutrition into a new mainstream of psychiatry, and his contribution in improving Taiwan's academic status and bringing benefits to patients.



2019 Award :
Professor Tin-Yun Ho

Professor Ho made valuable contributions in modern Chinese medicine and the biotechnology industry by analyzing a large amount of data from Chinese medicine research that was further applied to the development of biotechnology and pharmaceutical products.

China Medical University Hospital

A Pioneer in Cell Therapy

CMUH's "ADCV01 (Dendritic Cell) Cell Therapy" passed the examination of Special Regulation for Cell Therapy and was authorized by the Ministry of Health and Welfare. CMUH can now receive and treat 8 types of cancer patients.

Launch the "Cell Therapy Center"

Launched on June 18th, the Cell Therapy Center is accepting stage 4 patients with from 8 types of cancers. CMUH is constantly pursuing research innovation and breakthroughs. With the approval of special regulation for cell therapy from the Ministry of Health and Welfare, cell therapy is proved to be effective and this brings great news to patients.

"During the 10 years that CMUH has dedicated to cell therapy research, we have established GTP core cell operation room that conforms to the regulation of Cell Therapy Clinical Trial Practice. CMUH also has trained 165 qualified professional clinical doctors with the cell treatment qualification. On May 15th, CMUH was one of the first institutions to pass the examination from the Ministry of Health and Welfare that can receive and treat patients," said Chairman Chang-Hai Tsai.

In addition, the stem cell team lead by Vice-Superintendent Woei-Cheang Shyu has reached the international standard. Stem cells can be used to treat brain stroke and arthritis, and in the future the technology of cytokine-induced killer (CIK) cells treating solid tumor will be developed. The types of cancers that can be treated in the Cell Therapy Center will be further expanded, and more patients will be benefited.

In recent years, the healthcare quality of CMUH has been progressing rapidly. The launching of the Cell Therapy Center brings CMUH to a new era of cell treatment. In the future, CMUH Cell Therapy Center will bridge the clinical demand with industrial development, combine the upstream, midstream, and downstream medical markets and technology, and furthermore promote Taiwan's cutting-edge medical treatment to the world.

Exclusive Interview

Assistant Professor Peter Karl Mayer Acquired Taiwan (ROC) Naturalization

"I love Taiwan, and I'm very happy to become Taiwanese." Dr. Peter Karl Mayer, Assistant Professor of CMU School of Chinese Medicine, acquired Taiwan citizenship without renouncing his original German nationality. CMU President Mien-Chie Hung said the naturalization of Dr. Mayer symbolized CMU's hard work on internationalization. CMU not only provides opportunities for students and teachers to go abroad, but also recruits overseas talents to bring contribution to Taiwan's medical education.

Dr. Mayer's interest in Chinese culture started when he was 12 years old and met a Singaporean martial artist at his hometown in Germany. While studying in Giessen University, Dr. Mater was aspired by the profundity of Chinese acupuncture. Therefore, he came to Kaohsiung, Taiwan to study Chinese, and afterwards went to Shanghai, China to study acupuncture. However, Dr. Mayer realized that Taiwan is the place that inherited the traditional essence of Chinese medicine, therefore, he forwent his study in Shanghai.

Twelve years ago, with passion in Chinese acupuncture, Dr. Mayer came to Taiwan once again to fulfill his dream. Dr. Mayer obtained his master degree from CMU Graduate Institute of Chinese Medicine, and furthermore obtained the Chinese Medicine degree from the School of Post-baccalaureate Chinese Medicine. With relentless efforts, Dr. Mayer finally obtained the Chinese medicine practitioner license after completing his study. Now he serves as a training doctor at China Medical University Hospital.

Originally, Dr. Mayer planned to go back to Germany after completing his study, but eventually he fell in love with the life in Taiwan and decided to stay.

Dr. Mayer is one of the 10 overseas experts that acquired Taiwan citizenship on May, 2019, without having to renounce their original nationality. "This is a great progress. Now our basic needs for living in Taiwan is assured, we can focus on our professions and make contribution to Taiwan's society" said Dr. Mayer.

International Partnerships

A High-level Academic Exchange : The 2nd CMU-MU Joint Symposium

The 2nd China Medical University (CMU)-Mahidol University (MU) Joint Symposium was held in Taichung, Taiwan from January 2nd – 4th, 2019. President Banchong Mahaisavariya of Mahidol University led 12 faculty members to participate in the symposium; while 21 faculty members from China Medical University led by former Chancellor Wen-Hwa Lee, Vice-President Lu-Hai Wang, and the Dean of CMU Office of Global Affairs Liang-Yo Yang participated in this academic event.

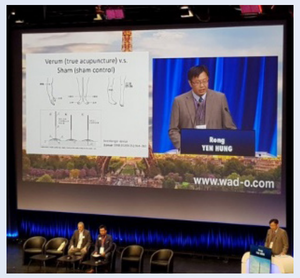
In addition to the discussion forum, 25 PhD students and postdoctoral research fellows from CMU presented their research in the poster session. The enthusiastic participation of academic talents from both universities had made the symposium a high-level academic feast.

In the symposium, professors from CMU and MU reached consensus in developing collaboration targets and topics in the field of precision medicine, Chinese medicine, neural science, pharmacy, and public health. Moreover, professors from both universities look forward to apply for joint cooperation grants in the near future.

Mahidol University, founded in 1890, is the most prestigious university in Thailand with two schools of medicine. With the organization of Dean Liang-Yo Yang, 7 professors from CMU attended the 1st CMU-MU Joint Symposium that took place in Thailand in January 2018. Since the 1st Joint Symposium, CMU and MU have already begun cooperating in various fields and the results are beginning to emerge gradually.

Acupuncture Shines on the World Stage: UNESCO Invited CMU Professor Hung-Rong Yen as the Guest Speaker

Dr. Hung-Rong Yen, the associate dean of China Medical University (CMU) College of Chinese Medicine, was invited as the VIP speaker at World Acupuncture Day. During the assembly, Dr. Yen talked about his research on Chinese medical treatment for fibromyalgia.



While delivering the speech, Dr. Yen discussed how Taiwan is not only preserving Chinese medicine tradition but is also carrying out scientific research in acupuncture. The research on Chinese medical treatment for fibromyalgia was highly recognized by the director of the World Acupuncture Day and a medal was given to Dr. Yen as a praise for Taiwan's high standard development in Chinese medicine and acupuncture research.

China Medical University's achievements in Chinese medicine and acupuncture has made CMU a star in the field worldwide. Former Chancellor Wen-Hwa Lee happily remarked, "CMU students and faculties are proud that Taiwan's soft power is being recognized internationally."

Professor Jaung-Geng Lin Published the English Version of "Experimental Acupuncturology"

Dr. Jaung-Geng Lin, an international renowned expert in acupuncture, was invited by the global publisher Springer Nature as the chief editor for the book "*Experimental Acupuncturology*". This book is the English version of the Chinese tool book for acupuncture. *Experimental Acupuncturology* featured the experiences and wisdom from 14 scholars and experts. It took five years of verification before the book was completed and now it will be published worldwide for acupuncture education. The publication of "*Experimental Acupuncturology*" will surely enhance Taiwan's international reputation in acupuncture.

2019 CMU-NUS Joint Symposium in Herbal Medicine and New Drug Development

China Medical University (CMU) and National University of Singapore (NUS) held the CMU-NUS Joint Symposium in Herbal Medicine and New Drug Development on April 24th, 2019. Professor Fred Wong, Head of NUS Department of Pharmacology, Professor Christina Chai, Head of NUS Department of Pharmacy, and Dr. Edward Chow from Cancer Science Institute of Singapore, participated in the symposium. They were invited by Professor Liang-Yo Yang, the Dean of CMU Office of Global Affairs. Over 50 CMU faculty and students enthusiastically engaged in the symposium.

"The best way to promote advances in science and technology is idea exchanges between scholars and researchers. This CMU-NUS joint symposium focuses on herbal medicine research, new drug development, and new drug development researches facilitated by AI. I hope this symposium not only enhances international academic exchanges and our friendship, but also strengthens our cooperation in scientific research", said President Mien-Chie Hung in his opening remarks.

Nine presentations by CMU and NUS faculty were delivered in the symposium. Representatives from both universities showed strong interest in each other's research topics and there were heated discussion after each session.

Moreover, both universities agreed to take the advantages of the research expertise of CMU's Research Center for Chinese Herbal Medicine, Drug Development Center, and NUS's Pharmaceutical Innovation & Research Centre. CMU and NUS will both invest more research resources and put efforts in developing anti-inflammatory drugs for asthma and arthritis, apply QPOP to sort out effective herbal medicine that can regulate immune function, and probe into the possible effects of acupuncture on patients with chronic obtrusive pulmonary diseases.

Dean Liang-Yo Yang Participated in 2019 Asia-Pacific Association for International Education (APAIE)

Professor Liang-Yo Yang, Dean of CMU Office of Global Affairs, participated in the 2019 Asia-Pacific Association for International Education (APAIE) on behalf of China Medical University. During the APAIE meeting, Dean Yang discussed the bilateral cooperation with the representatives from the National University of Singapore (NUS) and Nanyang Technological University (NTU). The cooperation will surely enhance the competitiveness of CMU in the international higher education market.

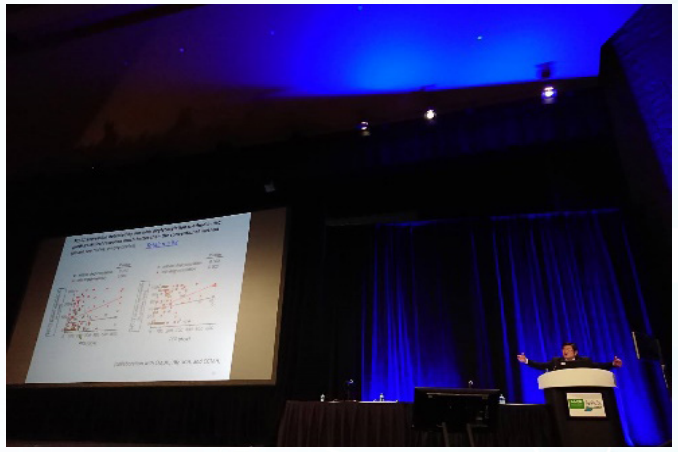
Dean Yang and the Associate Vice-President of NUS, Victor P. W. Shim, discussed about how NUS and CMU should strengthen the cooperation in the field of cancer, aging, neuroscience, and medical services. In addition, Dean Yang will be arranging a group of CMU professors and researchers to visit NUS and give lectures in the near future. The two schools also talked about research cooperation, short-term research program, and elaborate on the details of the 3rd CMU-NUS joint symposium.

Signing MoU with National University of Singapore (NUS)

Dr. Yap Seng Chong, the Dean of NUS Yong Loo Lin School of Medicine, visited China Medical University (CMU) on an academic exchange for three days in February 2019. Dean Chong signed MoUs with the CMU School of Medicine and the CMU School of Chinese Medicine, to enhance the international collaboration in teaching and medical research between NUS and CMU.

Dean Yap Seng Chong met with CMU Vice- President Lu-Hai Wang and discussed the cooperation between the two universities in the fields of cancer, neuroscience, aging, and Chinese herbal medicine. The two universities will strengthen their research cooperation on the topics regarding healthy aging, and will take turns to hold joint symposium annually.

American Association for Cancer Research (AACR) Invited President Mien-Chie Hung to Deliver a Speech at the 2019 Annual Meeting



President Mien-Chie Hung of China Medical University was invited to deliver a speech at the 2019 Annual Meeting of American Association for Cancer Research (AACR). President Hung is an expert in molecular biology and cancer research. In the meeting, he delivered a speech on the latest findings for cancer treatment "Critical role of glycosylation of PD-L1", which impressed the participating scientists with the rapid advancement of Taiwan's cancer research.

AACR is one of the largest cancer research conferences in the world. The main theme of 2019 meeting was "Integrative Cancer Science · Global Impact · Individualized Patient Care". Over 20,000 experts and scholars attended the conference to exchange thoughts and share their findings in cancer research.

President Mien-Chie Hung was one of the co-chairman of the 2017 AACR annual meeting. He has gained international reputation in the field of receptor tyrosine kinases and the molecular mechanisms of tumor progression. In addition, President Hung has made important contributions to the new signaling pathways in cancer cells, and recently developed an effective therapy targeting mechanisms and immune checkpoint inhibitors. Moreover, President Hung has been invited to participate in the editorial team of many international journals for cancer researches, such as *Cancer Cell*, *Cancer Research*, and *American Journal of Cancer Research* (AJCR). During the meeting of AACR, President Hung also attended the senior editorial meeting for *Cancer Research*, a journal of AACR, to gain the latest development of world's cancer research and personalized patient care service.

Uplifting Taiwan's Global Profile! President Mien-Chie Hung's Visit to the United States

Delivering a Speech at Harvard University

President Mien-Chie Hung headed to Beth Israel Deaconess Medical Center of Harvard University Hospital after the AACR meeting, and gave a lecture on the topic "Marker-Guided Target Therapy, PAPR and EGFR Inhibitors and Development of Effective Immune Checkpoint Therapy".

Recruiting Overseas Talents

President Mien-Chie Hung held talent recruitment meetings in Boston, Chicago, and Houston. While on the way to Chicago, the flight was forced to land in Iowa due to heavy snow. Being trapped in the airport, President Hung delivered the talk through video conference with students and it was indeed a unique and unforgettable experience.

President Hung believes that recruiting international faculty will bring new dynamics to CMU, broaden students' horizons, and promote the development of university affairs. In the talent recruitment meetings, President Hung illustrated the features and strength of CMU, and encouraged overseas talents to join CMU.

Attending the "Outstanding Lecture Forum" at Northwestern University

At the last stop of the US trip, President Hung was invited to give a talk at Northwestern University, Chicago.

At Northwestern University, President Hung attended the "Outstanding Lecture Forum" held by the PhD Student Association of the Cancer Center. In addition to delivering a speech on the topic "Marker-guided target therapy, PARP and EGFR inhibitors, and development of effective immune checkpoint therapy", President Hung also exchanged ideas and shared about Taiwan's medical research with the attendees.