CMU GLOBAL CONNECTION

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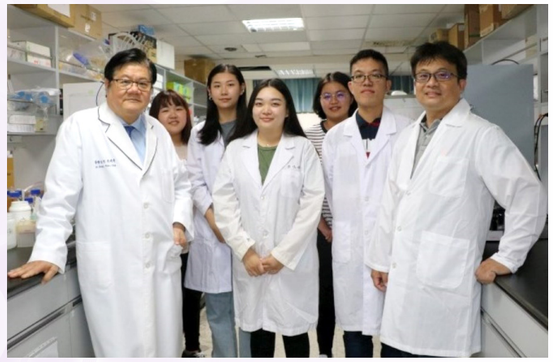
New Breakthrough in Taiwan's Anti-Pandemic Research!

CMU President Mien-Chie Hung and Research Team Publish SARS-CoV-2 Inhibitor Paper in *bioRxiv*



Scientists all over the world are now working hard to find vaccines for treating COVID-19. President Mien-Chie Hung of China Medical University, Taiwan, is leading a team studying how the strategies and concepts used in target therapy for cancer treatments can be used to combat COVID-19. They have screened more than a thousand FDA-approved drugs and were able to isolate inhibitors that could effectively inhibit the activity of the main protease of the coronavirus: Tafenoquine (TFQ).

Their paper "Inhibition of Severe Acute Respiratory Syndrome Coronavirus 2 Main Protease by Tafenoquine In Vitro" has been accepted by the American Chemical Society (ACS) and was included in *bioRxiv* (preprint server for Biology). This study again puts Taiwan front and center in the fight against COVID-19.

President Mien-Chie Hung stated that the replication and maturation of the coronavirus require the cleavage of the peptide through the main protease, to produce the core required for virus replication. The inhibitor Tafenoquine (TFQ) that the research team had screened is the first to prove that TFQ can induce significant conformational changes in SARS-CoV-2 Mpro protein, which will significantly reduce its protease activity.

The research team also cooperated with the National Taiwan University College of Medicine and many young scientists in China Medical University Hospital. Their research proved that TFQ is effective in inhibiting SARS-CoV-2 infected cells, which is expected to bring about great medical breakthroughs in the fight against COVID-19.

Taiwan has set an excellent example in the pandemic prevention of COVID-19. With the spirit of the medical profession, the research team of CMU is developing the cutting-edge medical research, and investing into the development of target drugs for COVID-19. "Once we find a treatment or vaccine for the COVID-19, thousands of lives can be saved. We have to work hard to succeed," said President Mien-Chie Hung confidently.

Research Findings Against the Pandemic

President Mien-Chie Hung and Research Team Publish the Structure of the SARS-CoV-2 Main Protease in Complex with the Inhibitor GC376 in *American Journal of Cancer Research*

A recent study published in *American Journal of Cancer Research* shows the potential for a significant breakthrough in fighting COVID-19. In a study using strategies and concepts of target therapy for cancer treatment and screening, CMU President Mien-Chie Hung and the CMU anti-pandemic research team found a core protease that can inhibit the replication of coronavirus.

The study entitled "Structural Basis of SARS-CoV-2 Main Protease Inhibition by a Broad-Spectrum Anti-Coronaviral Drug" was published in the August 2020 issue of *American Journal of Cancer Research* and was selected as the cover story. It has aroused great attention from international academic fields and medical institutions.

Following the discovery of TFQ (an inhibitor that can effectively inhibit the activity of main protease of the coronavirus), the finding of the core protease that can inhibit the replication of coronavirus provides strong evidence for further human clinical trials.

President Hung has been actively integrating the research team of CMU to fight COVID-19. From the thousands of small molecule compounds, the research team initially screened out the broad-spectrum inhibitor GC376 that can effectively inhibit the activity of the main protease of the coronavirus. In addition, Professor Ye Chen (Institute of New Drug Development) used the cutting-edge equipment to analyze the complex 3D structure of a potential drug and the main protease of the

virus. This is Taiwan's first 3D structure of the protease for the drug treating coronavirus.

President Hung explained, "The replication and maturation of the coronavirus require the cleavage of the peptide pp1ab/pp1a through the main protease to produce the core protease required for virus replication. Therefore, the inhibitor GC376 can simulate the substrate of the main protease of the coronavirus and bind tightly to its active site to inhibit virus replication."

Taiwan has set an excellent example in the pandemic prevention of COVID-19. With the spirit of medical profession, the CMU research team is dedicated to developing the cutting-edge medical research, and investing into the development of target drugs for COVID-19.

Face Masks Effectively Prevent the Spread of COVID-19: Professor Jong-Yi Wang's Letter Is Published in *Science*

Taiwan's prevention measures and public health strategies for COVID-19 are being recognized internationally. CMU Professor Jong-Yi Wang, Chair of the Department of Health Services Administration, had a letter published in *Science* discussing how Taiwan's mask-wearing policy effectively prevented the spread of COVID-19.

The letter published in the March 6, 2020 issue of Science, discussed that Taiwan used two strategies in the fight against COVID-19. These were the wearing of face masks and the checking of body temperatures. These two fairly easy and effective strategies helped keep Taiwan safe from the need for the lockdown and mass testing. Only those who have symptoms are tested, with only those with positive results going through self isolation.

The letter also discussed the quick work of the Central Epidemic Command Center of Taiwan, to ensure that masks were available. These included a face mask rationing plan along with expanding the face mask production lines. Taiwan has proved that face masks can help prevent the spread of the COVID-19 pandemic and allow cities to avoid lockdowns.

Combating COVID-19

CMU and NTU AIROBO Held the 2nd "Taiwan is Helping: AI x Pandemic Prevention Online Forum"

Taiwan has shown an outstanding performance in the prevention of COVID-19. On June 20th, 2020, China Medical University (CMU), Taiwan, and the Center for Artificial Intelligence and Advanced Robotics of National Taiwan University, held the 2nd "Taiwan is Helping: AI x Pandemic Prevention Online Forum," where topics of public health strategies, medical care, digital technology, along with testing developments and applications in the post-pandemic era were discussed.

Academician and the Taiwan former Vice-President Chien-Jen Chen, gave a keynote speech entitled "The Application of AI in Taiwan Epidemic Prevention." Dr. Chen emphasized that the key to the success of Taiwan's epidemic prevention lies in "the cautious attitude, rapid response, and advanced deployment."

During the address, Dr. Chen stated that "Technology innovation and caring for each other are the best ways to overcome the pandemic. Providing everyone with health care will promote a healthy living environment for all the people. Through mutual cooperation, we can definitely get through the pandemic situation."

Taiwan has world-class medical standards and modern technology. The government also supports the biomedical industry and focuses on the four key points: testing, developing vaccines, medical treatment, and medical materials. The goal is to build a national team for the epidemic prevention and make Taiwan shine on the world stage.

Chinese Medicine Experts in Taiwan and China Share Experiences of Combating COVID-19 through Video Conference

One of the ways to deal with the spread of COVID-19 is through Chinese medicine therapy and treatment. In order to further the discussion, a program entitled "Video Conference: Chinese Medicine Treatment in COVID-19" was held on May 14, 2020. Experts from China shared their experiences of applying Chinese medicine treat COVID-19. Experts from Taiwan shared the use of Chinese medicine in response to the pandemic, how Chinese medicine played an important role in the prevention and treatment in Taiwan's pandemic, along with the experiences of frontline nurses in the epidemic prevention.

Dr. Mao-Feng Sun, Dean of CMU College of Chinese Medicine, served as the co-host in the video conference. Dr. Sun discussed that even at the beginning of the outbreak in Wuhan, China has "successful cases of treating the COVID-19 through the combination of Western and Chinese medicine." These results lead CMU to create the "CMU Western-Chinese medicine cooperative team for treating the COVID-19." The group is actively conducting large scale screenings and evaluates the clinical efficacy of Chinese medicine for treating the COVID-19.

"We hope to find an effective treatment and make Taiwan's Chinese medicine be seen in the world," said Dr. Sun, who also added that "Chinese medicine is a treasure left by our ancestors for thousands of years, and it can certainly make a contribution in fighting the COVID-19."

Another participant was Dr. Hung-Rong Yen, Associate Dean of CMU College of Chinese Medicine, who has worked with professors from China, Japan, and South Korea. Dr. Yen also published "Traditional Chinese Herbal Medicine for Novel Coronavirus (COVID-19)" in the March 2020 issue of *Japan Medical Journal*. This article helped introduce the use of Chinese herbal medicine to fight COVID-19 to the Japanese medical community.

Outstanding Awards

23rd Moscow International Salon of Inventions and Innovative Technologies "ARCHIMEDES": 2 Gold Medals & 1 Silver Medal

China Medical University, Taiwan, made a splash at the 23rd Moscow International Salon of Inventions and Innovative Technologies "ARCHIMEDES" (2020) by winning two gold medals along with one silver medal.

Professor Liang-Yo Yang (Gold Medal): Assembleable Artificial Medical Implants

A medical implant composed of artificial bone plate units that can be used for surgical repair of skull defects or craniofacial and maxillofacial reconstruction. In clinical application, it has very convenient composability and operability in treating skull, craniofacial, and maxillofacial defects, which can effectively save a lot of surgical operation time.

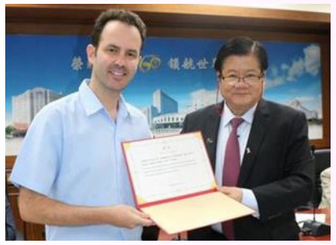
Professor Chung-Ming Liu (Gold Medal): The Application of Plasma Sterilization System for MRT Cabin

A system that can be used to sterilize and deodorize MRT carriages. The system uses high electric field plasma which not only sterilizes and deodorizes air, but also does not affect air circulation. The system can effectively eliminate bacteria and smells in the carriages to provide a safe and comfortable space for passengers.

Professor Lih-Jyh Fuh & Professor Chung-Ming Liu (Silver Medal): Innovation of Natural Coral Application on Injectable Bone Graft

The team transformed coral into a calcium phosphate structure, and combined it with fluid calcium sulfate, allowing it to be used in dental and orthopedic bone repair through injection. In addition, it has natural porous structure so it has better compatibility and strength than other artificial porous ceramics. According to the research results, MedCoral Injectable Bone Graft has great operability and biosafety. Presently, an academic-industry cooperation project is set to complete various analyses and the results will be used to apply for relevant certification.

International PhD Student Gil Ton Was Awarded "Taiwan Scholarship Graduate Student Outstanding Performance Award"



Dr. Gil Ton came to Taiwan with his family to pursue his PhD degree in acupuncture at CMU in 2015. Besides his study in acupuncture, Dr. Gil Ton also enhances his Chinese ability and has passed the advanced level of TOCFL (Test of Chinese as a Foreign Language).

Since 2019, Dr. Gil Ton was hired as an adjunct lecturer in the School of Chinese Medicine, teaching Chinese medicine and acupuncture related courses in English. Dr. Gil Ton lived up to the expectation of a Taiwan Scholarship awardee, made the most of every penny of his scholarship, and made himself shine in the field of acupuncture.

CMU Ranked the 2nd Best Private University in "Taiwan's Best University Ranking" by Global Views Monthly

CMU has been working hard on cultivating talents and connecting with prestigious universities and institutions worldwide. CMU ranked the 2nd among private universities in the 2020 Taiwan's Best University Ranking.

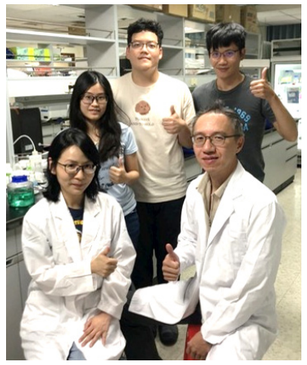
Among the different indicators in the evaluation, CMU ranked the 4th in teaching performance, 2nd in the number of college student research projects awarded by the Ministry of Science and Technology, and 3rd in the number of research papers published in the peer-reviewed international journals.

Research Breakthroughs

A New Treatment Direction for Drug-resistant Breast Cancer! CMU Research Team Publish in *Nature Communications*

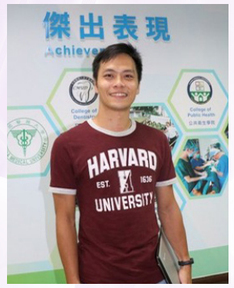
A group of physician scientists led by Dr. Chun-Ju Chang and Dr. Jer-Yen Yang have made a breakthrough discovery. By analyzing breast cancer genes, they found that TET2 plays a key role in breast cancer development and cell differentiation, and this finding can provide a new direction for the diagnosis and treatment of drug-resistant breast cancer. Their research "TET2 Directs Mammary Luminal Cell Differentiation and Endocrine Response" was published in the September 15, 2020 issue of *Nature Communications* and has received high attention from the international medical community.

Among breast cancer patients, 80% of them are estrogen receptor-positive (ER+) with hormone therapy applicable. However, it is very common for ER+ patients to develop drug resistant to hormone treatment. The research team found that 15%-20% of drug resistance comes from DNA methylation, which leads to the low or loss of ER expression. DNA demethylation enzyme (TET2) is an important epigenetic regulatory factor and is associated with human cancers. Therefore, the research team established TET2 deletion mouse model and revealed that TET2 plays a pivotal role in mammary gland development and cell differentiation. TET2 deletion-PyMT breast cancer mouse model exhibits enhanced mammary tumor development with deficient ER expression that confers tamoxifen resistance.



The research team also discovered that TET2 and FOXP1 form a chromatin complex that co-dominates the DNA demethylation and gene expression of the three genes: ESR1, GATA3, and FOXA1. These three genes are of great importance for the luminal cell differentiation, and in basal-like breast cancer, these genes are often DNA methylated. As a result, the lack of TET2 gene will cause the low expression of ESR1, GATA3, and FOXA1, thus hindering the differentiation of breast stem cells into luminal cells (ER+), so that breast stem cells can only differentiate into drug-resistant substrate cells.

This study showed that the low expression of TET2 can be used as an important indicator to predict human breast cancer cells' resistance to hormone therapy. The increase of TET2 expression and activity have the potential to become a new treatment direction for drug-resistant breast cancer patients.



Positive News for Obesity and Diabetes Patients! CMU Dr. Chih-Hao Wang Publishes in *Science Translational Medicine*

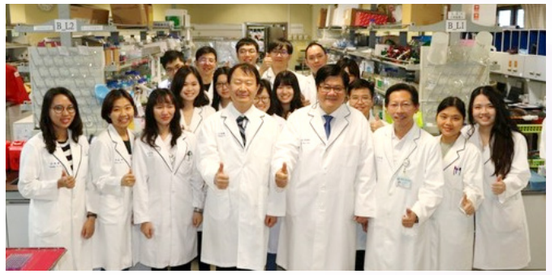
Dr. Chih-Hao Wang, CMU Graduate Institute of Biomedical Science faculty, and Harvard Medical School Postdoctoral Fellow, published "CRISPR-engineered Human Brown-Like Adipocytes Prevent Diet-Induced Obesity and Ameliorate Metabolic Syndrome in Mice" in the August 2020 issue of *Science Translational Medicine.* Dr. Wang's research team successfully used CRISPR-Cas9 technology to engineer human white adipocytes to display brown fat-like phenotypes, which may open up cell-based therapeutic opportunities to combat obesity and diabetes.

Dr. Wang's research team engineered human white pre-adipocytes using CRISPR-Cas9–SAM–gRNA to activate endogenous uncoupling protein 1 (UCP1) expression, and created human brown-like (HUMBLE) cells. HUMBLE cells possess the function of human brown cells. In addition, studies of the HUMBLE cells transplantation in immunocompromised mice have shown effective energy expenditure and weight loss, and improvement in glucose tolerance and insulin sensitivity.

White fat is for energy storage, while brown fat can consume extra energy. Clinical Studies have shown that in human adults, brown fat with high metabolic activity has the potential to fight obesity. Dr. Wang explained, "Among obese patients, the amount of brown fat is very low, but the amount of white fat is high. Thus, our research created brown fat from white fat to treat obesity, and increase energy consumption and blood glucose regulation. This can be a potential technology to treat metabolic disorders."

A New Strategy for Target Therapy of Liver Cancer! CMU President Mien-Chie Hung Publish a New Strategy for Treating Liver Cancer in the *Journal of Hepatology*

President Mien-Chie Hung's collaborative research team published "Ribonuclease 7-Driven Activation of ROS1 is a Potential Therapeutic Target in Hepatocellular Carcinoma" on October 4, 2020 in the *Journal of Hepatology.* This research discovered the key role of the orphan receptor ROS1 protein RNase7 in the treatment of liver cancer, which could provide a new strategy for the target therapy of liver cancer. This could help patients extend their survival time.



Hepatocellular carcinoma (HCC) is the most common type of primary hepatic carcinoma. The existing small molecule kinase inhibitors approved for treating HCC can only prolong the survival period of patients by a few months, so it is urgent to find effective biomarkers and new alternative therapies.

Receptor tyrosine kinase (RTK) plays a key role in regulating cell differentiation, proliferation, migration, and angiogenesis. The disorder of RTK signals will lead to many types of cancer development. ROS1 is the last orphan receptor with kinase activity in the RTK family, however, its ligand is still unknown. In addition, its functions in cell function regulation and disease development remain unclear. To this end, President Hung's team screened a variety of Ribonuclease (RNase) family proteins and found that RNase7 specifically binds to the N3-P2 domain of the extracellular region of ROS1. RNase7 stimulation can lead to the phosphorylation of the terminal tyrosine residue site Y2274, which activates the signaling pathway of ROS1.

By establishing the primary hepatic carcinoma mouse model and the xenograft model of HCC, the authors found that inhibition of RNase7-induced ROS1 activation can significantly slow down the tumor growth and prolong the life span of the mice. The team then analyzed the expression levels and the clinical data of ROS1 and RNase7 in HCC patients, and found that those with high ROS1 and RNase7 expression were highly associated with poor survival period and tended to have a recurrence of cancer. Such patients are expected to benefit from the treatment with ROS1 inhibitors to prolong their survival period. RNase7 has a great potential to function as a biomarker to stratify HCC patients for anti-ROS1 treatment, which of course can provide an important reference for clinical treatment strategies.

CMU Vice-President Fuu-Jen Tsai's Clinical Research Team Publish in The *Journal of Clinical Endocrinology and Metabolism*

CMU Vice-President Dr. Fuu-Jen Tsai and his clinical research team have made a new discovery in the genetics of familial short stature of Han Chinese ancestry in Taiwan. The study "Genetic Architecture Associated With Familial Short Stature" identified 10 novel genetic single nucleotide polymorphisms (SNPs) and 9 reported GWAS human height-related SNPs that lead to the risk of familial short stature. The research was published in the May 2020 issue of *The Journal of Clinical Endocrinology and Metabolism.*

The study compared 1163 participants of Han Chinese ancestry diagnosed with familial short stature (FSS), to a control group of 4168 individuals with no FSS history. A polygenic risk predisposition score for FSS risk prediction was developed by investigating the FSS genetic profile of both groups.

"Human height is an inheritable, polygenic trait under complex and multilocus genetic regulations. One of the most difficult topics in genetic research is an increase in height, because its influences are too complicated. Genetic predisposition to human height has been widely explored using GWAS in multi-ethnic populations. FSS is the most common type of short statures, but its genetic profile remains poorly understood," said Dr. Tsai, who has profound experience in predicting children's height by bone age assessment.

Since FSS can only be caused by genetic factors, there is 90% accuracy in using genetic loci to predict whether a child has the risk of short stature. Further research will be carried out on the human height prediction, along with investigations into the mechanism and control of human growth. With scientific research and proper treatment, there is hope that growing taller will become possible in the future.