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China Medical University's Research Breakthroughs

A New Strategy for Targeted Treatment of Tumors: President Mien-Chie Hung's Recent Research Breakthrough Is Published in *Nature Cell Biology*



China Medical University President Mien-Chie Hung and MD Anderson Cancer Center (Texas) have solved the mystery of the molecular mechanism of tumor pyroptosis. The collaborative research team published their research findings "PD-L1-mediated gasdermin C expression switches apoptosis to pyroptosis in cancer cells and facilitates tumor necrosis" [doi: 10.1038/s41556-020-0575-z] in *Nature Cell Biology*, which provides a new strategy for the targeted treatment of tumors.

Pyroptosis, an innate immune response of fighting pathogens, mainly occurs in macrophages of the immune system. The pathogens will stimulate the Caspase-1 hydrolyzed molecule-the GSDMD of Gasdermin family, and ionize the N-terminal structure to bind to the cell membrane to form holes of 10-14 nanometers. Once the cell membrane is destroyed by the holes, it will cause death to the cell due to the changing osmotic pressure. This is a typical process of pyroptosis. However, in addition to macrophages, whether pyroptosis occurs in tumor cells and cancer development remains unclear.

Tumor necrosis is a common pathological phenomenon and is mainly caused by the rapid growth of tumors.

The excessive size leads to hypoxia. Although this phenomenon has been known for more than 100 years, the exact cause, molecular mechanism, and whether pyroptosis is involved are still unsolved mysteries.

By screening a variety of common tumor stimuli, the research team found that a hypoxic environment can induce a large number of PD-L1 molecules to enter the nucleus, and that Stat3 phosphorylated under hypoxic environment can combine with PD-L1 to enter the nucleus together. In the nucleus, the complex formed by PD-L1 and phosphorylated Stat3 will bind to the GSDMC promoter to promote the expression of GSDMC protein, which differs from the key molecule GSDMD of the typical pyroptosis that occurs in macrophages. In the tumor microenvironment, TNF- α will activate the Caspase-8 of cancer cells, hydrolyze GSDMC, separate the N-terminal and bind it to the cell membrane, and eventually cause the cell to burst and die. This research shows that the mechanism of pyroptosis induced by tumor cells and its key molecule GSDMD is very different from the typical mechanism.

This study first revealed the unknown PD-L1 nuclear function. In clinical application, by screening the commonly used tumor chemotherapy drugs, researchers found that the antibiotic chemotherapy drugs can induce triple-negative breast cancer MDA-MB-231 cell strains to go pyroptosis, showing that pyroptosis may play an important role when treating triple-negative breast cancer by chemotherapy drugs.

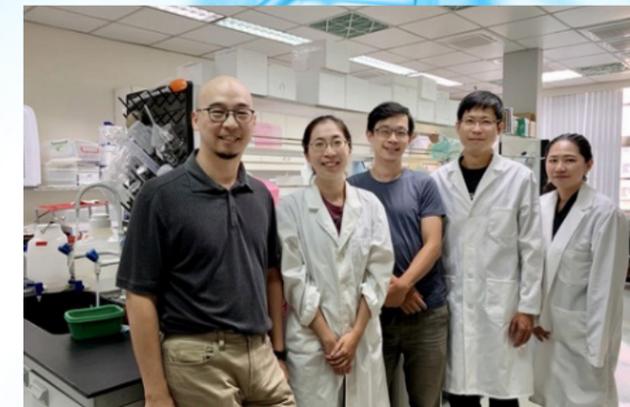
"The specific performance of GSDMC in tumor cells is the best biomarker. If drugs can be used to induce cancer cells to undergo pyroptosis to destroy tumors, this will surely become a brand new and highly potential precision medicine strategy," said President Mien-Chie Hung.

Professor Ao-Lin Hsu Publishes Research Findings in *Science Advances*

A major breakthrough in the research of the longevity gene. CMU Professor Ao-Lin Hsu (Center of Excellence for Healthy Aging) led a research team that discovered the genes that control the life clock, and found the molecular mechanisms of HSF1 and HSB1 proteins in delaying aging and prolonging life spans. Their research findings "HSB-1/HSF-1 pathway modulates histone H4 in mitochondria to control mtDNA transcription and longevity" [doi: 10.1126/sciadv.aaz4452] is published in the prestigious journal *Science Advances*.

In the past 16 years, the CMU Center of Excellence for Healthy Aging has been working hard to find the longevity and aging genes that control the life clock and the speed of human aging. The research team was trying to understand the roles of these genes in regulating the speed of aging at the cellular and molecular levels. The team discovered that when HSF-1's inhibitory protein HSB-1 is eliminated, the aging speed will be significantly delayed, leading to prolonged life span in animals. Further, the expression of histone H4 in the cells of these animals is higher than usual.

Histone H4 is one of the main components of nucleosome in the nucleus, so it is generally believed to appear in the nucleus only. However, Professor Ao-Lin Hsu's team discovered that in the cells of their long-living animals, histone H4 also appeared in the mitochondria. Histone H4 binds with mitochondrial DNA (mtDNA), regulating the gene expression of mtDNA to affect mitochondrial function. In addition, HSF-1/HSB-1 and



other longevity genes can also increase the stress resistance of cells and delay aging with the same method.

This research not only revealed the molecular mechanism of HSF-1 and HSB-1 proteins in delaying aging and prolonging lifespan, but also provided the latest evidence that histone H4 can be transferred to mitochondria under certain conditions to perform different functions.

In the application of translational medicine, this research provides an excellent benchmark for the development of anti-aging drugs in the future. Professor Hsu expects that if an effective HSB-1 protein inhibitor can be developed, there might be a possibility of developing new anti-aging strategies that can prolong the "healthspan" of human beings to achieve the goal of "healthy aging."

CMU Research Team and Georgia State University Publish Findings of a Collaborative Research on "PRMT1 as a Therapeutic Target in Neuroblastoma"

Neuroblastoma is a type of malignant tumor and is the most common extracranial solid tumor in children. It is also the 4th most common cancer in children, with around 30-40 cases in Taiwan each year. What makes neuroblastoma difficult to treat is that it has very diverse manifestations, and the cause of occurrence is still unclear.

The research team of Dr. Xing-Guo Lee from CMU Graduate Institute of Biomedical Sciences has been contributing to the molecular biology research on neuroblastoma from a variety of aspects for many years. To find a novel and safe treatment for neuroblastoma, the team is also collaborating with Georgia State University Department of Pharmaceutical and Biomedical Sciences.



Recently, the research team discovered a new role of the protein PRMT1 in the pathogenesis of neuroblastoma. Moreover, they found a small molecule compound "diamidine" that can effectively inhibit the growth of neuroblastoma. Their research findings received great attention from the medical community and were published in two prestigious journals that focus on oncology research: *Oncotarget* and *Oncogenesis*.

After the research was published, Dr. Xing-Guo Lee's research team was funded US \$100,000 by the Rally Foundation for Childhood Cancer Research for the pre-clinical trial. "With the funding for doing clinical trial, we hope that the new treatment can be completed as soon as possible so that more children can be benefited," said Dr. Xing-Guo Lee excitedly.

CMU and UK Collaborative Research Team Publish Review Paper Discussing the Role of Omega-3 Fatty Acids in Mental Healthcare during COVID-19

The international collaborative team of Dr. Kuan-Pin Su (CMU), Dr. Pei-Chen Chang (CMU), and Dr. Carmine Pariante (King's College London) published the world's first paper review about "Omega-3 fatty acids in the psychological and physiological resilience against COVID-19" [doi: 10.1016/j.plefa.2020.102177] in *Prostaglandins, Lipids, and Essential Fatty Acids*, the official journal of the International Society for the Study of Fatty Acids and Lipids.

Many reports have shown that during the pandemic, the prevalence of anxiety, depression, and post-traumatic stress disorder have increased. Currently, the pandemic situation of COVID-19 is still severe worldwide, with vaccinations just beginning. In addition to protecting oneself from COVID-19, people are concerned about how to reduce the anxiety caused by the pandemic.

The CMU Mind-Body Interface Research Center has been dedicated to the research of nutrition in the prevention and treatment of brain and physical diseases, and the mechanism of Omega-3 fatty acids and immune regulation. This publication discussed the role of Omega-3 fatty acids in combating the mental problems caused by COVID-19.

"The critical period of COVID-19 lies in the first two weeks after infection. If the patient's innate immunity can detect the virus in the shortest time and successfully block the virus in the upper respiratory tract, the



patient's clinical manifestations may be similar to those of asymptomatic infection, which greatly reduces the chance of developing into severe illness. This is because Omega-3 fatty acids have the function of enhancing our innate immunity, so the harm of COVID-19 can be reduced," said Dr. Chang.

The fight against COVID-19 continues and will be a long struggle. Immunity is closely related to our physical and mental health. Long-term stress may lead to pathological tension and affect the immunity against viruses. Therefore, Dr. Su suggested that we get regular exercise, have a healthy daily routine, have enough sleep, and reduce excessive information that can lead to anxiety. "Keeping a healthy lifestyle and positive thinking will help in maintaining a good health condition."

Assistant Professor Yen-Liang Liu Publishes Research Findings in *ACS Nano*



CMU Assistant Professor Yen-Liang Liu published the study "Three-Dimensional Two-Color Dual-Particle Tracking Microscope for Monitoring DNA Conformational Changes and Nanoparticle Landings on Live Cells" [doi: 10.1021/acsnano.9b08045] in the international journal *ACS Nano*.

Single-particle tracking (SPT) has enabled direct observations of particle dynamics with sub-millisecond temporal resolution and submicron spatial resolution inside complex biological systems. With decades of efforts, SPT has provided insights into actions of motor proteins, dynamics of cell membranes, transport of mRNA, internalizations of viral particles, searching mechanisms of DNA-binding proteins on the genome, ligand-induced endocytosis of membrane receptors, and intermolecular interaction of virus-like nanoparticles to transmembrane receptors.

Most of the SPT techniques today focus on monitoring the translational dynamics of particles. Until recently, Dr Yen-Liang Liu and his collaborators at the University of Texas at Austin developed a three-dimensional two-color dual-particle tracking (3D-2C-DPT) technique which is able to perform 5-dimensional tracking (x, y, z, and two rotational angles). This technique enabled us to investigate the DNA bending kinetics in a free solution as an optical ruler.

Furthermore, they demonstrated the capability of monitoring the landing of an antibody-conjugated nanoparticle on the plasma membrane of living cells. This study revealed that the interactions between antibodies and EGFRs confined the translational and rotational motions of tracers. These results demonstrate that our 3D-2C-DPT technique is a powerful tool to study the conformational changes of biomolecules and the intermolecular interactions on plasma membrane.

International Collaboration

CMU and Fulbright Taiwan Sign A Memorandum of Understanding

The Fulbright exchange program is the most iconic international exchange program in the United States, with a total of 49 foundations and 110 embassies operating worldwide. In November 2020, CMU and Fulbright Taiwan signed a Memorandum of Understanding and agreed to form an international academic talent exchange network that will connect scholars and institutions worldwide.

CMU will be promoting its distinctive Chinese medicine and acupuncture program, so that American students can come to Taiwan to study and gain experiences. Three programs will be offered: short-term courses, a program for master's degree, and a program for American Fulbright scholars to do exchanges in Taiwan.



International Cooperation in Chinese Medicine: A Memorandum of Understanding Signed between CMU and Mae Fah Luang University



China Medical University Dean Mao-Feng Sun (College of Chinese Medicine) signed a Memorandum of Understanding with Mae Fah Luang University (Thailand) in a virtual meeting. The agreement aims to produce Massive Open Online Courses (MOOCs) in Chinese Medicine and to promote exchanges and cooperation between the two universities. The two universities are currently developing four MOOCs:

1. "The Wisdom of Traditional Chinese Medicine in Life" offered by CMU
2. "Aromatherapy Massage" offered by Mae Fah Luang University
3. "Chinese Medicine Acupuncture" co-offered by CMU and CMU Hospital
4. "Understanding Chinese Herbal Medicine" co-offered by CMU and Mae Fah Luang University

Professor Wu-Chung Shen Publishes the English Version of Textbook entitled *Diagnostic Neuroradiology: A Practical Guide and Cases*

Professor Wu-Chung Shen was invited by the internationally renowned publisher Springer Nature to compile the English version of *Diagnostic Neuroradiology: A Practical Guide and Cases*. This textbook consists of Professor Shen's 40-year teaching experiences, and includes more than 2,000 CT and MRI illustrations from clinical cases. It also features a wealth of concise diagnostic tips for common brain and spine diseases and serves as a valuable reference guide for clinical diagnosis. The English version of *Diagnostic Neuroradiology* will be published worldwide for medical education and will surely promote Taiwan's international status in the field of neuroradiology.

Professor Shen has been involved with the teaching for the interpretation of medical imaging for 40 years.



He has also published many practical textbooks. Moreover, Professor Shen takes use of the modern technology and combines it into his teaching at very early stage. The teaching website he established is a popular learning resource for many medical students.

"In the past two years, compiling this book has brought a focus to my half-retired life. Now I still guide the clerks in image interpretation every week, and I also run a teaching website open to medical students, doctors, as well as people who understand Chinese in the world. I will add the content of *Diagnostic Neuroradiology* to my website and include case descriptions, and I hope to pass on my valuable experiences to the young doctors and medical students," said Professor Shen.

Outstanding Awards

Professor Shih-Chieh Hung Receives the 16th Excellent Medicine & Technology Award

Professor Shih-Chieh Hung and the research team of the CMU Drug Development Center have worked tirelessly in research and clinical application of using mesenchymal stem cells in the treatment of degenerative arthritis and other diseases. Their research “Mesenchymal stem cells in regenerative medicine and application of cell therapy and disease translation” was honored with “The 16th Excellent Medicine & Technology Award” by the Tien Te Lee Biomedical Foundation.

“We used the tumor tropism of mesenchymal stem cells to carry tumor lytic viruses to treat cancer, and used peptides to carry diagnostic reagent, hyaluronic acid, and stem cells, to assist in the diagnosis, lubrication, and regeneration of degenerative arthritis. We hope that our research can be used in clinical treatment in the near future. Once it is applied in clinical use, it can bring benefits to patients and promote the development of cell therapy industry,” said Professor Hung.



CMUH Chief Executive Long-Bin Jeng’s Team Receive the 2020 FutureTech Demo and Breakthrough Award



The cross-disciplinary team of CMU and National Chiao Tung University received the “2020 FutureTech Demo and Breakthrough Award” for their research technology “Low-dose nanoscale biomimetic cell structure—Next-generation platform technology for advanced precision immunotherapy.” This research combines nanotechnology into the concept of immune bionics, and develops an artificial immune system with fucoidan nano magnetic structures, which successfully improves the immunity in tumors and prevents tumor metastasis and recurrence. In addition, this innovative technology can greatly shorten the course of treatment and simplify the administration of drugs, providing a better way than adoptive cell therapy. With its scientific breakthrough, this technology received very high appraisal by the Award Committee.

“We not only found that fucoidan nano structures are bionic, but also provided new functions to the bionic structures after integrated nanotechnology. This technology can obtain a more comprehensive immune response through intravenous administration, which surpasses the current complicated process of culturing T cells in vitro. Moreover, it can alter the treatment combination according to the patients’ individual differences. This is certainly an important milestone of the technology breakthrough of Taiwan’s immunotherapy,” said Chief Executive Long-Bin Jeng.

Professor Suh-Hang Juo Receives the “Excellence in Technology Transfer Award” from the Ministry of Science and Technology for Developing Novel Eye Drops for Treating Myopia

The patent for novel eye drops for treating myopia developed by the research team of CMU Professor Suh-Hang Juo has been successfully transferred to Sunhawk Vision for continuing development. For the work, Professor Juo received the “Excellence in Technology Transfer Award” from the Ministry of Science and Technology.

The goal of Professor Juo’s research team is to develop new eye drops to treat children with increased myopia. The eye drops developed by the team have won National Innovation Award and Future Technology Award, and the research team was selected as a highlight project team by the MOST.

Presently, Sunhawk Vision had commissioned the biotechnology industry to conduct the final preclinical trial. It is expected that the drug certificate can be obtained soon and the eye drops can enter the Asian market where there is high prevalence of myopia.



China Medical University and Healthcare System Participate in 2020 Taiwan Healthcare+ Expo

At the opening ceremony of the 2020 Taiwan Healthcare+ Expo, President Ing-Wen Tsai of Taiwan remarked that 2020 is a challenging year due to the COVID-19 pandemic. The government will continue to expand the interdisciplinary advantages of the healthcare industry, and support the digital transformation of the healthcare industry to make Taiwan a center for the digital medical transformation in the world.

The theme of China Medical University and Healthcare System in the exhibition was “Medical Technologies & Digital Health.” The booth focused on 4 major themes: Cell Therapy, Artificial Intelligence, Multi-Dimensional Printing, and Precision Medicine. It displayed the highlights of CMU’s latest smart medicine, the cutting-edge medical research, and the features of the innovative medical technology.



In addition, a specially designed AI interactive experience section was set up so that the public could participate in the AI interaction activity. CMU is looking forward to promoting the precision healthcare industry, and making a significant contribution to the society.

Following the trend of digitalization, the medical team of China Medical University Hospital has been actively developing smart medicine and biomedical innovative technology, and cooperates with the world-renowned medical centers to seek breakthroughs. The research teams of China Medical University and China Medical University Hospital received a total of 11 National Innovation Awards in 2020, showing that CMU’s outstanding research performance is highly recognized.

CMU Beigang Hospital Receives the “13th Taiwan Corporate Sustainability Awards”



CMU Beigang Hospital was honored with a Bronze Medal, at the 13th Taiwan Corporate Sustainability Awards, in the category of the “Circular EcoBest Sustainability Project Awards-Hospital.”

CMU Beigang Hospital received the award due to the efforts in providing professional and friendly healthcare.

CMU Beigang Hospital upholds the spirit of “a quality medical service” and is a “friendly hospital,” promoting comprehensive medical services to the rural community. In addition to providing medical care, the medical personnel of CMU Beigang Hospital also established a dining hall for the elderly, as well as a LOHAS station for health promotion. Moreover, the hospital works with a dance group to provide art therapy.

CMU Beigang Hospital not only allows the elderly in Yunlin County to live a healthy and happy life, but also connects them to the world through the sustainable development goals of the United Nations.

“Better Life, Better World!” CMU Receives the 2020 National Sustainable Development Award

CMU actively engages in long-term care for the elderly, protection for the environment, food and drug safety, diseases prevention, and the care for the local high schools and community. With plentiful fulfillment in the university’s social responsibilities, CMU was honored with the 2020 National Sustainable Development Award.

The main campus of CMU at Shuinan was the only campus in Taiwan to receive the “Building Carbon Footprint Certificate” from Low Carbon Building Alliance (LCBA), and both the “Smart Building” and “Green Building” certificates from the Taiwan Architecture & Building Center.

CMU is working hard in cultivating talents, solving medical problems, teaching, and researching in the field of medical care. With the spirit of “Better Life, Better World,” President Mien-Chie Hung leads CMU to become a world-class university and is committed to making efforts and contributions to Taiwan’s sustainable development.

