A PATH TO A HEALTHY FUTURE

Fundamental and translational research at the CHINA MEDICAL UNIVERSITY in Taiwan reveals crucial insights for cancer mechanisms, informing the development of precision medicine.

To combat a disease as complex as cancer, bridging the gap between fundamental studies on cancer biology, and the exploration of effective therapies is pivotal. Pushing new boundaries in understanding of cancer cells, China Medical University (CMU) in Taiwan and its affiliated hospital, CMUH, have been exemplary in bench to bedside synergy.

Translational discoveries on cancer biology

CMU's cancer research programmes are led by its president, Mien-Chie Hung, a world-renowned cancer biologist who has discovered novel signal transduction pathways in cancer cells. Focusing on developing marker-guided cancer therapies to improve patient care, Hung has directed his teams to unveil cancer mechanisms, and translate them to clinical advances.

In their studies on immune checkpoint regulation, much attention was devoted to PD-L1, a promising target in cancer therapy. The protein is known for its role in suppressing the immune system, achieved by interacting with a protein on T cells called PD-1. Hung's group showed that the immunosuppression activity of PD-L1 is modulated by glycosylation, an enzymatic process important for interactions between proteins. By suggesting pathways to regulate PD-L1 and block PD-L1/PD-1 interaction, their study shed light on potential therapeutic strategies. They developed a combination therapy to downregulate PD-L1, and achieved a survival rate of 50-70% in mouse models.

The team also identified other mechanisms underlying immunosuppression by PD-L1 glycosylation, including the way in which PD-L1 glycosylation is initiated. This improved knowledge helps redefine the microenvironment for tumour sensitization to immunotherapies, and unveil key targets to overcome drug resistance in advanced tumours.

Amplifying the potential for many of these projects, joint programmes between CMU and the University of Texas MD Anderson Cancer Center (MDACC) have been continuing since Hung left his management role at MDACC for CMU. In 2018, a joint study identified novel ligands in the blood of cancer patients that activate pro-tumour receptor tyrosine kinases (RTKs), proteins essential in cellular processes including growth and differentiation. The results suggest a serum biomarker that can be used to stratify patients for targeted therapies.

More recently, a collaboration between scientists at CMU, MDACC and Zhejiang University discovered a metabolic programming mechanism, triggered by cancer-causing signal genes, that links the generation of glucose and lipids with the progression of hepatocellular carcinoma (HCC), the most common type of primary liver cancer. These findings on cancer mechanisms could contribute to personalized medicine for cancer patients.

Surgical success on liver cancer

Also focusing on liver cancer, surgical oncologist, Long-Bin Jeng, who heads the CMUH Organ Transplantation Center, works to improve treatment through innovative surgical techniques. A leading clinician in hepatic transplantation, Jeng has performed more than 1,000 living donor liver transplantation (LDLT) surgeries in the past two decades. To prevent rejection of organ transplants, he used the chemotherapy drug, everolimus, as an immunosuppressant, and is considered a leader in this practice. Other pioneering work to improve LDLT also includes using multiple artificial blood vessels during transplantation, and introducing hepatic artery connection surgery. Jeng also conducted the world's first simultaneous liver and kidney transplantation involving multiple living donors.

To alleviate pain, Jeng's team promotes minimally invasive procedures, and completed more than 800 laparoscopic liver resection surgeries.

Through Jeng's efforts, five-year survival rate of liver transplant patients at CMUH, has reached 73%, and the rate for liver cancer patients is 61%.

Jeng is also exploring immune oncology to improve treatments for liver cancer patients. Overseeing CMUH's cell therapy taskforce, Jeng worked with CMU's spin-out company, Ever Supreme Bio Technology, to conduct Taiwan's first multicentre clinical trials on dendritic cell vaccines for glioblastoma, a rare cancer of the brain.

Progress in cell therapy and nanomedicine

Jeng's colleague, Der-Yang Cho, CMUH superintendent, is also working on the trial. As a neurosurgeon, Cho has formed a multidisciplinary group to integrate state-of-the-art neurosurgery with immune cell-based therapy. A phase II clinical trial on the vaccine for glioblastoma is now complete. Riding on that success and numerous publications advancing understanding of the tumour immune microenvironment, Cho's team is working with the government to strengthen Taiwan's competitiveness in cell therapy, with an act newly implemented for clinical application.

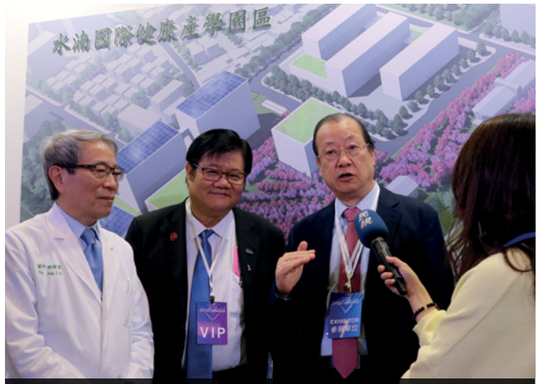
The CMUH team also works on developing autologous cell therapy, which involves using a patient's own T cells and natural killer (NK) cells, genetically engineering them outside the body to make the cells express a chimeric antigen receptor (CAR) designed to recognize a specific tumour antigen. This allows immune cells to target the cancerous cells, minimizing damage to the body. Clinical trials of the CAR-T and CAR-NK therapies for multiple cancer types are expected to be launched soon.

Another neurologist at CMU, Woei-Cherng Shyu, also a physician scientist, specializes in treating stroke and cardiovascular failure. With biophysicists, Shyu has developed an innovative nanomedicine that tackles the problem of immunosuppression in tumour microenvironment. With a fucoidan-based nanoparticle, conjugated with checkpoint inhibitors and immune stimulants, the drug's therapeutic efficacy can be further enhanced by magnetic navigation, presenting high potential for advanced cancers that are treatment-resistant.

Working on unravelling the roles of adult stem cells in diseases, CMU orthopaedic surgeon, Shih-Chieh Hung, has identified novel markers and specific signal pathways in cancer stem cells. He also revealed the epigenetic regulation of stem cell differentiation and oncogenesis, and the pathological involvement of mesenchymal stem cells in ankylosing spondylitis, a type of arthritis in the spine, causing long-term inflammation.

Medical research and clinical successes of CMU, demonstrated by publications in leading journals, such as *Nature*, *Nature Medicine*, *Nature Nanotechnology*, and *Cancer Cell*, rely on strong collaboration between the academic and clinical wings of CMU. Rigorous cancer research programmes have gathered multidisciplinary researchers from CMU's colleges of medicine, Chinese medicine, dentistry, pharmacy, medical engineering, public health, health care, and the newly established College of Life Sciences and Biomedical Engineering. This reaps the benefits of advancements in molecular and cell biology, genetic and epigenetic studies, system and structural biology, and imaging technologies.

A supportive cancer research environment is also empowered by CMUH, one of Taiwan's medical hubs of cancer treatment, which houses 6,000-plus beds for patient care, providing rich clinical resources. Various centres have been established, bringing together researchers and clinicians, and accelerating bench-to-bed translation. ■



Chang-Hai Tsai, MD, PhD; Chairman, CMU and its affiliated medical system (at right)


Mien-Chie Hung, PhD; President, CMU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