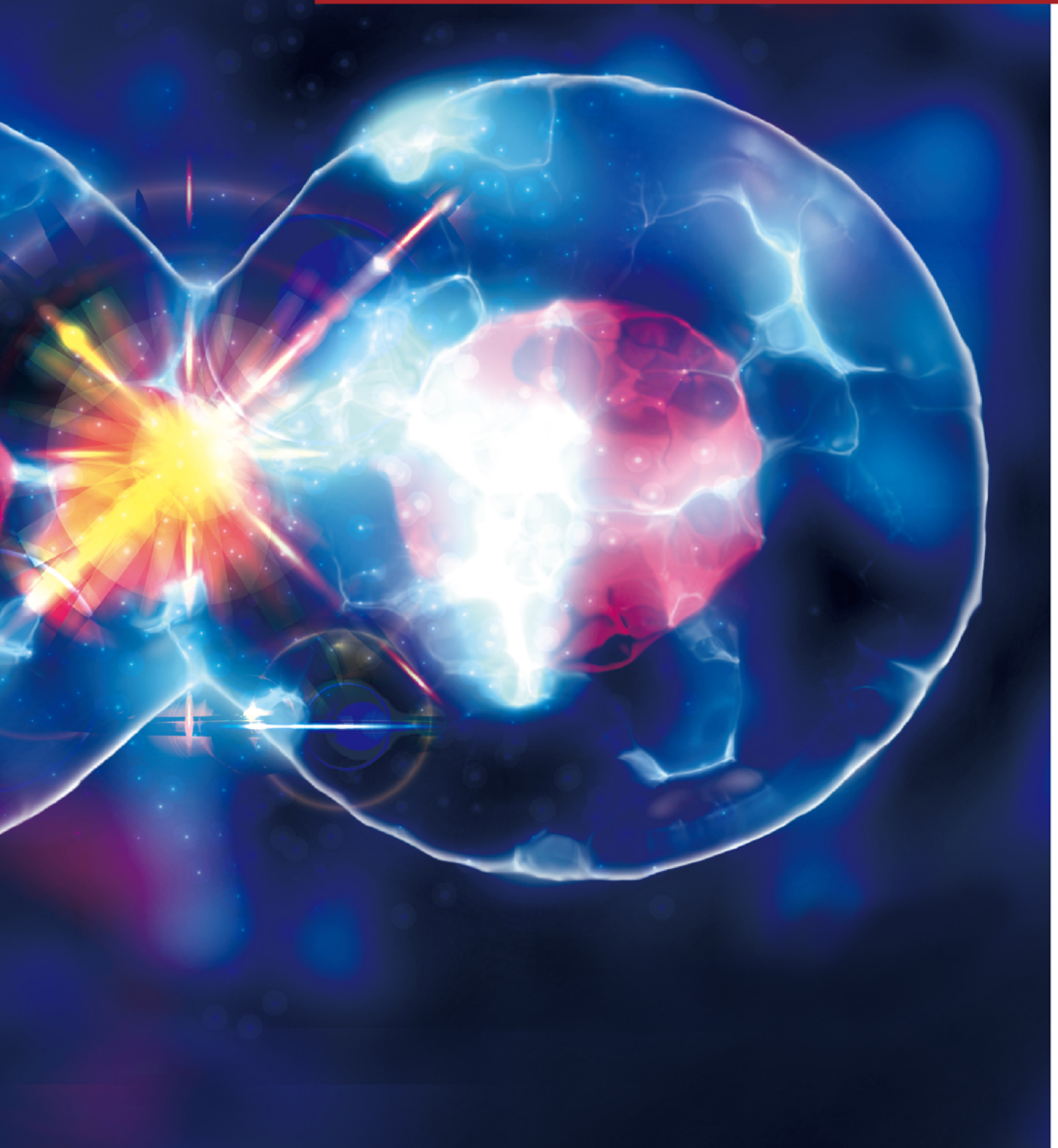


TIME SPOT LIGHT



2020 SUMMER



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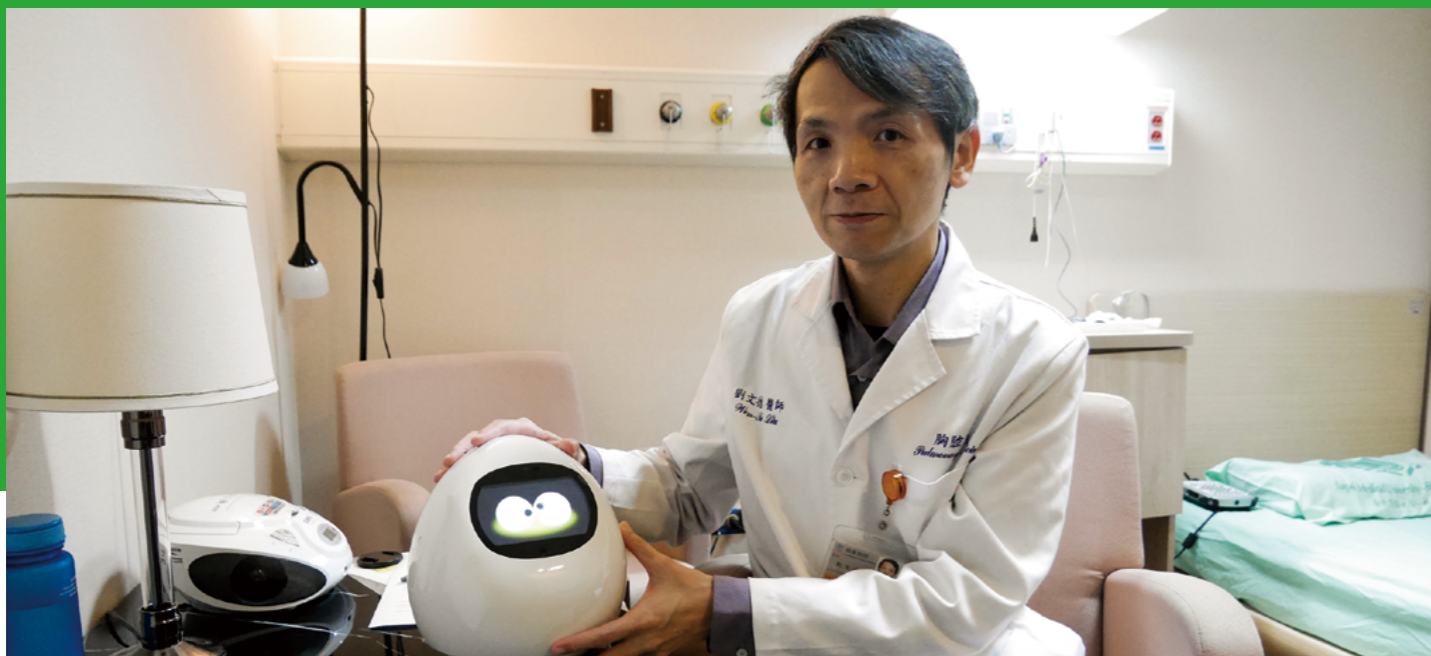


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IoT and Sleep Medicine:

changing paradigms, changing lives moving treatment from the hospital to the home



If you are a snorer, tired during the day, hoarse in the morning, or have to wake up at night to visit the bathroom, you might be suffering from sleep apnea. It is a common problem – perhaps half of patients seeing a GP will have some level of sleep apnea - that can have serious complications. Sleep apnea is correlated with elevated risk of heart disease and stroke, and has recently been linked to Alzheimer's disease.

The good news is the condition is usually treatable with lifestyle modifications or a ventilator, but hospital based testing is expensive and time consuming, and according to research by Dr. Wen-Te Liu, traditional hospital-based diagnosis may not be as accurate as previously thought.

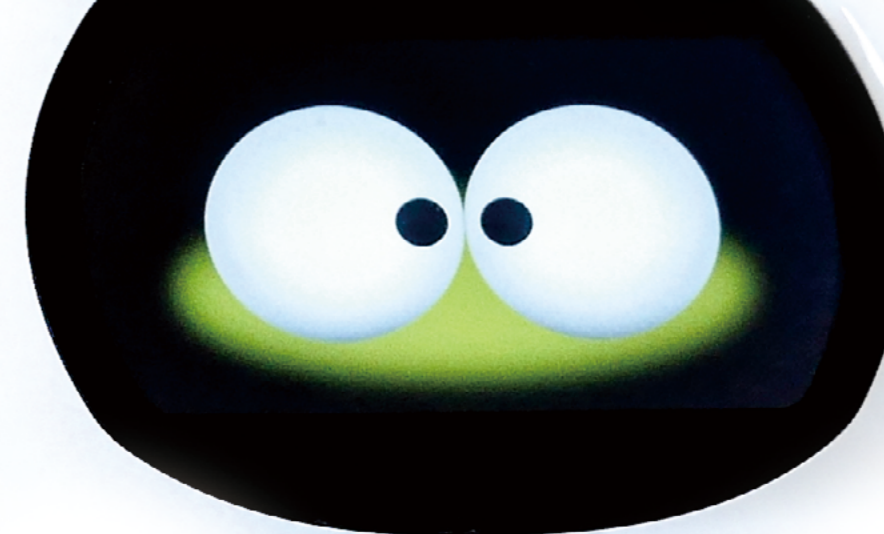
The problem of accurately and efficiently measuring the factors that affect sleep and creating effective treatment programs is TMU's sleep medicine expert is looking to address, and to do it he is making use of booming developments in internet-of-things (IoT) devices and artificial intelligence.

Sleep apnea is a dysfunction of the autonomic nervous system where muscles in the back of the throat relax and block the airway, temporarily stopping breathing. When the brain detects a low blood oxygen level, it briefly wakes you up to kick-start breathing. The process is often too quick to notice, and that can happen dozens of times each hour.

Traditional sleep medicine diagnosis involves doctors subjecting patients to a battery of questions before sending them for a night in the sleep lab. Researchers previously expected that sleep apnea would be underestimated in the lab due to sleeping in a strange environment connected to wires. But research published by Dr. Liu last year actually showed that the so called "first night" effect may actually result in the condition being overestimated in the lab, probably because patients connected to so many wires that they are forced to sleep lying on their backs and can't change their positions, which increases sleep apnea severity.

Dr. Liu wanted to predict sleep apnea severity without relying on hospital based tests. He began by gathering body profile and other medical parameters and came up with a prediction model that was 70-80% accurate. "Maybe it's because the patients' condition varies in the hospital, so I thought we need to test patients' sleep apnea in their home," said Dr. Liu.

Advances in artificial intelligence tools and the IoT now make home-based measurements possible. Dr. Liu is now undertaking a four-year study project that incorporates lab and home based measurements of patients' sleep quality using wearables and IoT sensing devices to create a comprehensive sleep apnea prediction model that allows individualized precision treatment strategies.



The first step is to streamline preliminary information gathering. Instead traditionally spending up to 90% of the time asking patients questions, the preliminary questionnaires can be automated using an interactive chatbot program on a web- or mobile-based app.

In the second phase, the chatbot can gather data on voice quality and cognitive function. As a snorer himself, Dr. Liu felt hoarse after a poor night's sleep, and he also saw many patients with persistent cough and hoarseness caused by snoring which led to the idea that voice could be as an indicator of sleep disturbance. The patient's voice can be recorded using a cellphone app, and the AI system can determine neurocognitive function at the same time.


Voice and neurocognitive data combined with other parameters can be recorded using wearables and home-based IoT devices that gather physiological and environmental data to account for factors that affect sleep quality like physical activity, air quality, noise, light, and temperature. In the third phase all the information is integrated and analyzed using AI tools to help create cognitive behavior therapy programs and sleep environment interventions.

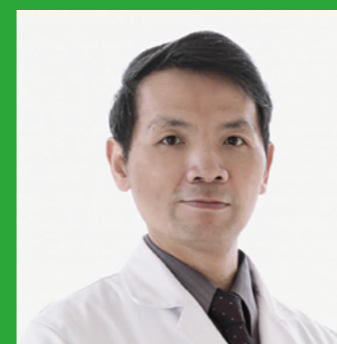
In designing his model Dr. Liu is taking advantage of its access to data from over 10,000 patients in northern Taiwan. He has already successfully uncovered links between

physical profiles, environmental pollution, and sleep disorders. As his AI model takes shape, a comprehensive sleep disorder prediction model is on the horizon.

Dr. Liu says that as sensing technology and data processing tools improve, doctors will be freed up to spend more time on patients, whether they have complicated clinical problems or would benefit from minor lifestyle changes. "When we developed some system or machine to take over the 'low level' task ... we can find how to improve patients' and peoples' health. In 200 years of medical science we just have the resources to focus on the severe problems."

Besides providing patients with longitudinal follow-up, the smart devices used to monitor severe sleep apnea can also be useful for people with subclinical issues. Dr. Liu is also working with business to build a personalized care program for anyone to upload their own data for analysis by his AI model.

A large proportion of sleep disturbances can be addressed through lifestyle changes, but whether a patient's condition can be improved by sleep hygiene or a sleep apnea ventilator, sleep data gathered in Dr. Liu's program will be a valuable resource for research and precision treatment, and will help move sleep studies to where sleep actually happens – out of the hospital and into the bedroom. 



Wen-Te Liu

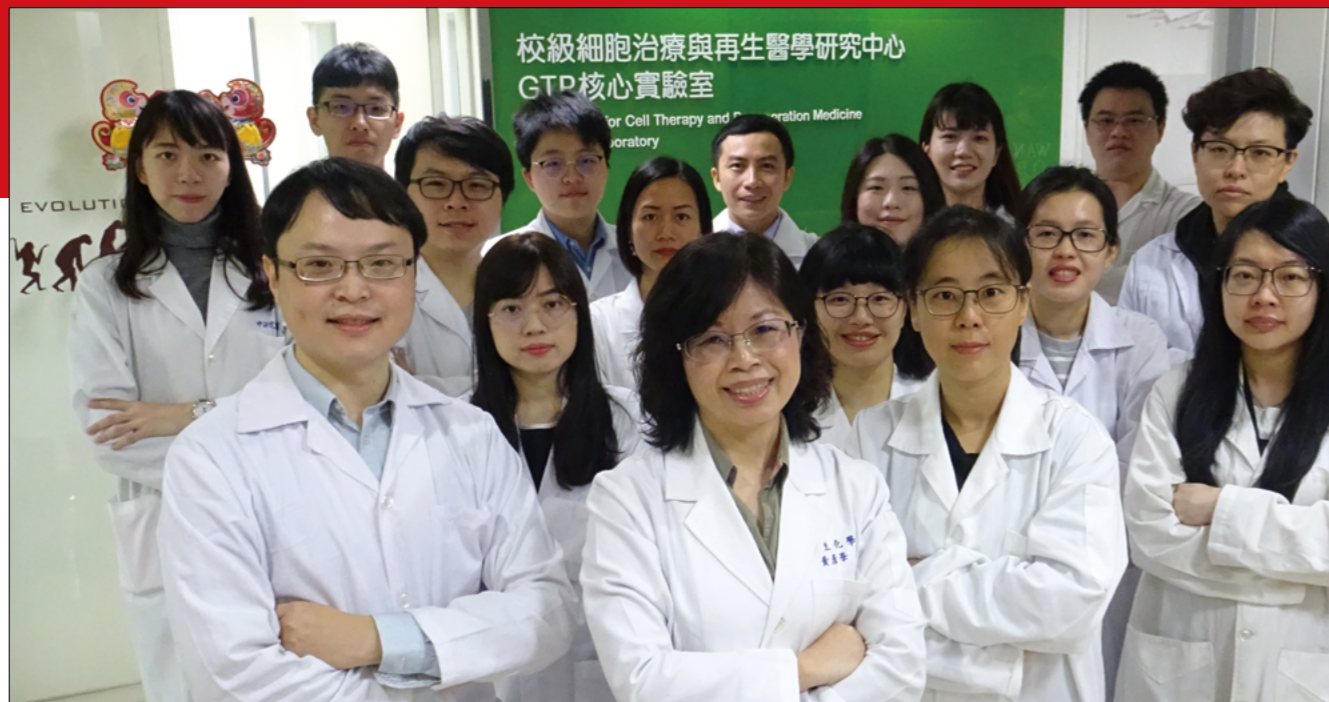
Doctor, Department of Chest Medicine, Taipei Medical University-Shuang Ho Hospital, Ministry of Health and Welfare.

Associate Professor, Professional Master Program in Artificial Intelligence in Medicine, College of Medicine.

Assistant Professor, Department of Internal Medicine, School of Medicine Associate Professor, School of Respiratory Therapy



Breakthroughs in Niche Microenvironments and Systemic Safety Therapeutic Cell Product Development



Two-time winner of Taiwan's Ministry of Science and Technology Outstanding Young Scientist Incubation Research Grant and holder of two stem cell related patents, Dr. Rita Yen-Hua Huang has made quite a name for herself as a star researcher. After 20 years of studying embryonic pluripotency, cancer stemness and cell therapy products, Dr. Huang brings her expertise to TMU Research Center for Cell Therapy and Regeneration Medicine and the GTP Laboratory to focus on the development of systemic safe and effective cell therapy products. Dr. Huang and her team are considered global leaders in the field and have developed a novel culture method to generate the stem cells with systemic safety and efficacy both in research and clinical treatments.

Niche microenvironment will affect cell fate dominantly. In cancer study, Dr. Huang looked at the critical role of inflammatory microenvironment in tumor pluripotency and recurrence in patients with liver cancer with and

without Hepatitis B. Because the Hep-B virus persists in the body long-term, patients display higher levels of the inflammatory IL-6 cytokine. The researchers found that in patients with HBV – and thus higher IL-6 levels – cancers were more likely to spread.

"If the microenvironment changes, stem cells will transform to cancer stem cells, or cancer cells will get reprogramming to express stemness then migrate easily, metastasizing and causing drug resistance. So, treatment fails or a patient relapses early," says Dr. Huang. This has important implications for treatment because patients found to have high levels of IL-6 can be given IL-6 neutralizing antibodies – or even aspirin, which is anti-inflammatory – and should have improved prognoses.

As scientists look to stem cells for research and new clinical treatments, understanding how niche microenvironment affects stem cell growth and differentiation is becoming

critical. To insure they keep their original characteristics – and to avoid tumor promotion risk – cells must undergo repeated passages with symmetrical division to produce quantities necessary for large-scale use.

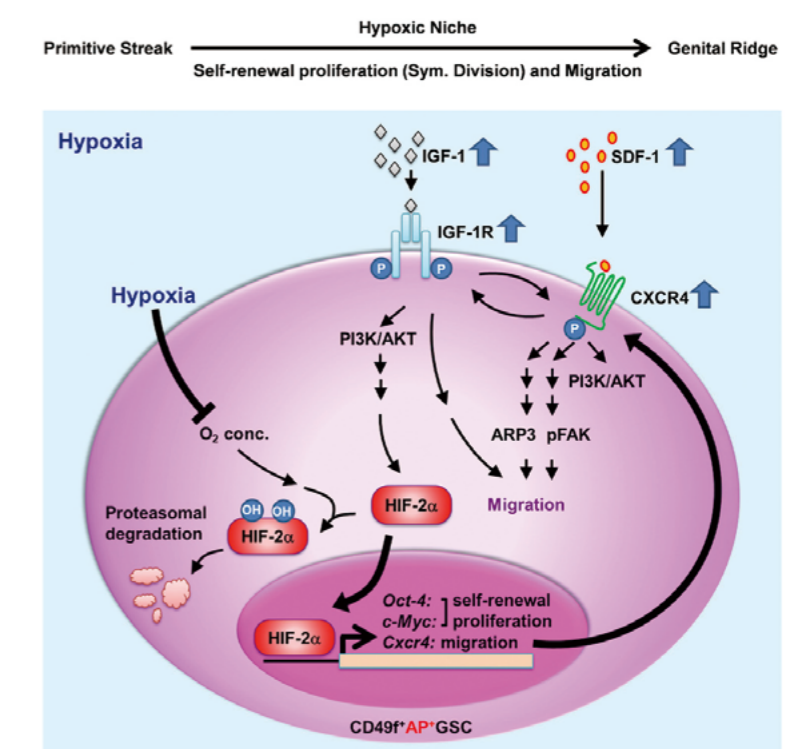
This is where some groups have run into problems. Osiris Technologies, for example, had promising early successes with Prochymal, an IV administered mesenchymal stem cell (MSC) product designed to treat children whose bodies reject bone marrow transplants that was cleared for use in Canada and New Zealand. Although Prochymal successfully completed Phase 1 and Phase 2 clinical trials, a large-scale Phase 3 trial unfortunately failed.

"The cells may differentiate and age," suggests Dr. Huang. "There is devil in the cell preparation. They had to generate so many cells for a lot of patients. They lost cell quality, the epigenetics changed and the cells differentiated." Osiris Technologies offloaded the product in 2013.

Seeing the weakness of corporate R&D programs, Dr. Huang began working on growing large numbers of stem cells without having them differentiate and being aged. Looking at embryonic germline stem cells, she and her team identified specific niche micro-environmental factors that play a critical role in the symmetric division and migration of embryonic germline stem cells.

In their study published in Stem Cell Reports, the team cultured pluripotent germline cells in a unique serum-free culture platform. By manipulating oxygen levels and monitoring crucial stemness protein levels, they were able to demonstrate that hypoxia cooperated synergistically with IGF-1R signaling to regulate stem cell symmetric division, proliferation, and cell migration.

Generating identical stem cells may be a delicate and difficult to control process, but now says Dr. Huang, "We know what environment and when the signal transduction can stimulate embryonic stem cells and MSCs to

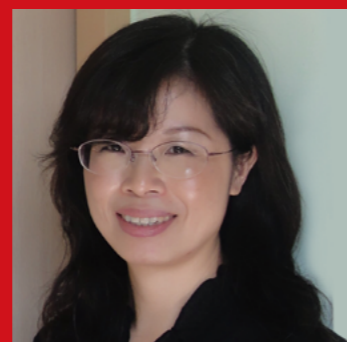


go into symmetric division. Now we can generate a lot of symmetrically dividing MSCs for clinical use.”

The team received 2019 The 16th National Innovation Award for their work, and Dr. Huang’s third patent is expected later this year.

“We can have a really beautiful SOP. We control cell quality, we know cell safety, we know the genetics, the transcriptome data, single cell sequencing, before and after cell responses to different kinds of injury on microenvironment. We can generate a lot of symmetrically dividing and systemic safety mesenchymal stem cells for clinical use.”

With a better understanding of cell culture protocols stemming from these discoveries, the allogeneic safety clinical grade MSCs from specific placenta tissues can now be produced in large numbers at TMU’s GTP lab. Under her special protocol, cells retain stemness, and can exceed 25 successful passages (cells in most other methods die off after 10). Importantly for patients, the cells are systemic safety and free of tumor risk which do not initiate or promote tumor growth. The allogeneic MSC cell therapy clinical trial targeting COVID-19 acute respiratory distress syndrome (ARDS) now is submitting to FDA for review. 🏠



Dr. Yen-Hua Huang

Distinguished Professor and Dean, Office of Research and Development
Executive Director, TMU Center for Cell Therapy and Regeneration Medicine
Director, Good Tissue Practice Lab.
Professor, International Master/Ph.D. Program in Medicine, College of Medicine
Professor, International Ph.D. Program for Cell Therapy and Regeneration Medicine

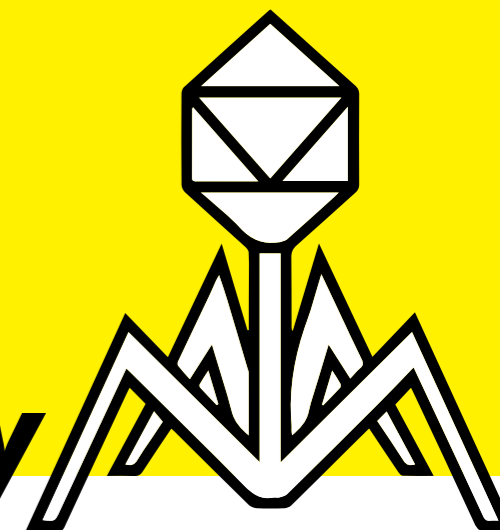
Winner of a number of prestigious research awards, including the MOST Outstanding Young Scientist Research Grant and the Outstanding Basic Research Award for Cancer Medicine, Dr. Huang holds patents for two stem cell processes with another to be awarded this year.



DO YOU KNOW?

Researchers trying to generate stem cells for use in clinical settings run into two main difficulties. One is generating a useful amount of cells; over repeated rounds of passage (growing cells over generations), the primary cells will differentiate, age and eventually die. Another is that cells’ “stemness” (their ability to self-renew, differentiate, and proliferate) itself is not always a good thing; under certain conditions stem cells can transform into cancer cells, or to promote tumor cell proliferation, or cancer cells can get reprogramming ability to develop stemness themselves – allowing them to easily metastasize and develop drug resistance. Targeting niche microenvironment is always the critical point for both the cancer treatment (tumor niche) and the systemic safety stem cell product development (culture niche).

A Path to Phage Display



Dr. Yi-Yuan Yang graduated from TMU with a degree in medical technology in 1983. He went on to earn a Master’s in biochemistry, and a PhD in Biology/Molecular Biology at Utah State University for the study of Bluetongue Virus in 1992. But after a long period working in virology, Dr. Yang was looking to branch out to something new; he moved to University of California in San Diego to take a post-doc position doing research on autoimmune diseases.

At the time there were two major ways to make antibodies. The traditional hybridoma technique of isolating antibodies from immortalized B cells through purification tedious fusion and screening steps. It was a powerful process that led to a 1984 Nobel Prize in Medicine and Physiology. But it’s not without certain drawbacks, like taking 4-6 months to produce useful amounts of antibodies and requiring extra steps for antibody humanization. Looking to find so-called “bad antibodies” behind autoimmune diseases, the UC San Diego group ran into problems when trying to produce antibodies using hybridoma technique. Dr. Yang’s advisor (Dr. Po-Jen Chen) therefore suggested a new technique involving fusing proteins to a viral shell that was first described in 1985 and under significant development at the Scripps Research Institute. With his advisor’s support, Dr. Yang was off to Scripps to become an expert in “phage display” technology.

In phage display, filamentous M13 bacteriophages (bacteria-attacking viruses) are genetically engineered to present a protein that can bind with a specific target. A specific antibody molecule “displayed” on the bacteriophage makes it able to attach to a target antigen. Then unspecific binders are washed out and antigen-specific phages are amplified. After several rounds of a bio-panning process are repeated, monoclonal antibodies with virtually any specificity can be isolated. The major difference between phage display and hybridoma technologies, says Dr. Yuan, is that “phage display uses molecular biology to clone the gene of the antibody from the antigen-primed B-cell. It’s a gene-level rather than cell-level technique”.

The technique has already been used to develop monoclonal antibody treatments like humira, which has sales of over 20 billion USD as of 2018 and is used for autoimmune conditions including arthritis and Crohn’s disease.

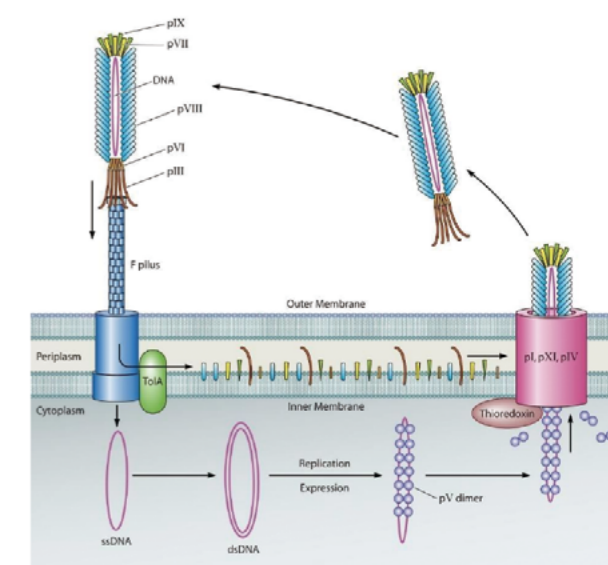
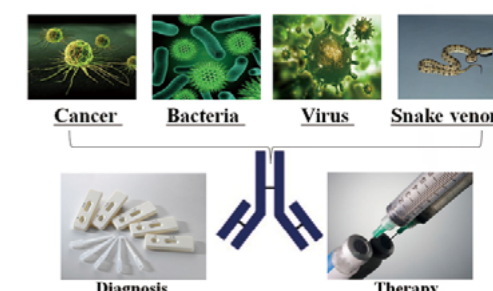
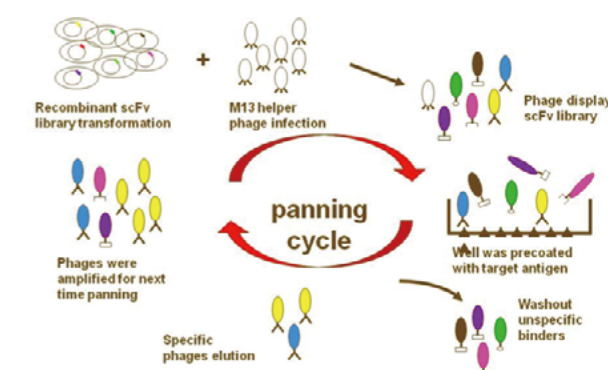
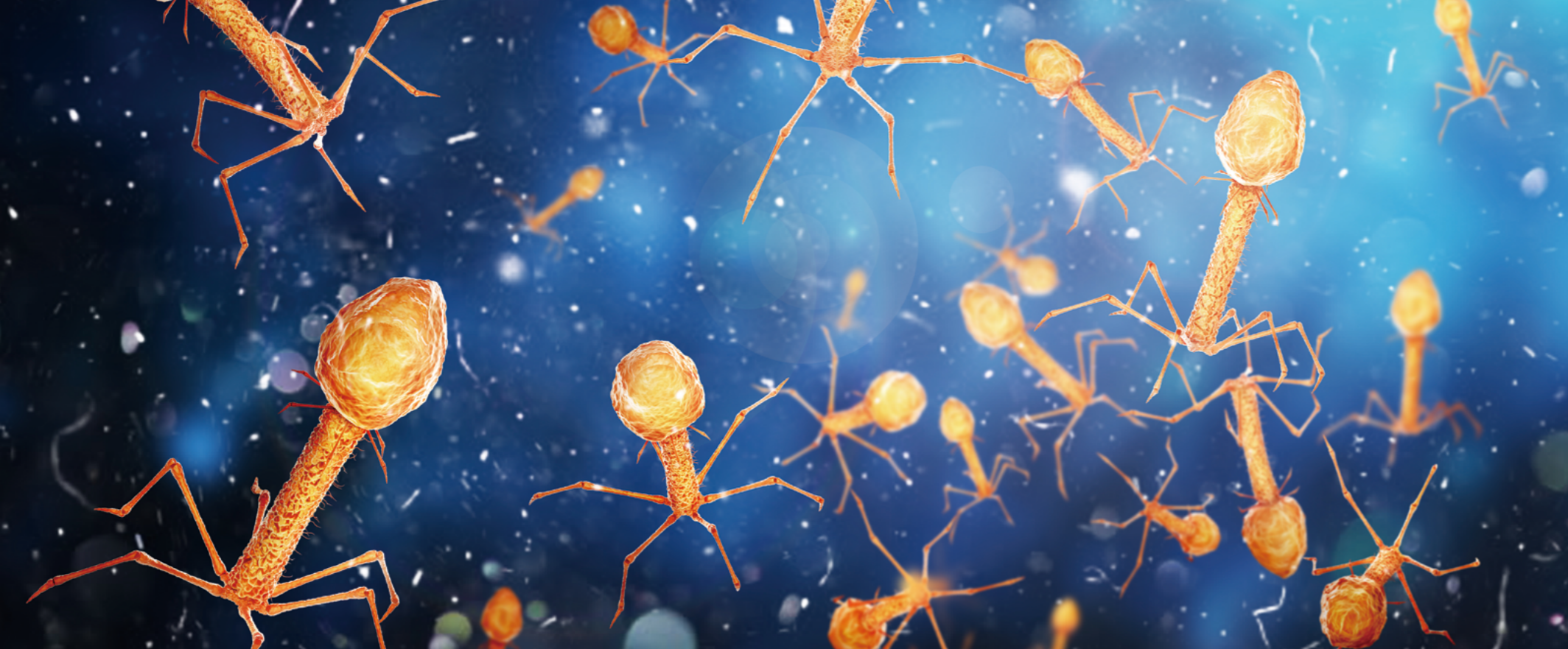


Fig 1. The life cycle of filamentous phages. (Huang, Bishop-Hurley and Cooper 2012)





Indigenous Research: SARS, Snakes, and Cancer

When recruited to TMU in 1994, Dr. Yang had earned a reputation as a researcher in time for the SARS scare in the early 2003. With Taiwan and the world facing the “terrifying” danger of an airborne epidemic, Dr. Yang was assigned by then TMU President Chung-Yi Hsu to work closely with Wanfang Hospital and the Department of Medical Laboratory Science to explore possible diagnosis and treatments.

Using his knowledge of phage display techniques, Dr. Yang successfully constructed several phage antibody libraries that could be used for diagnostics and therapeutic treatments. Luckily SARS did not become a global pandemic, but Dr. Yang’s work published in 2007 both provided a basis for further SARS research and showed the viability of using phage display technology to produce mono-specific antibodies with high specificities from immunized chickens^{[1], [2]}.

1. Lee YC, Leu SJ, Hung HC, Wu HH, Huang IJ, Hsieh WS, Chiu WT, Hsieh MS, Cheng TF and Yang YY*. (2007) A dominant antigenic epitope on SARS-CoV spike protein identified by an avian single-chain variable fragment (scFv)-expressing phage. *Vet Immunol Immunopathol.* 117:75-85.

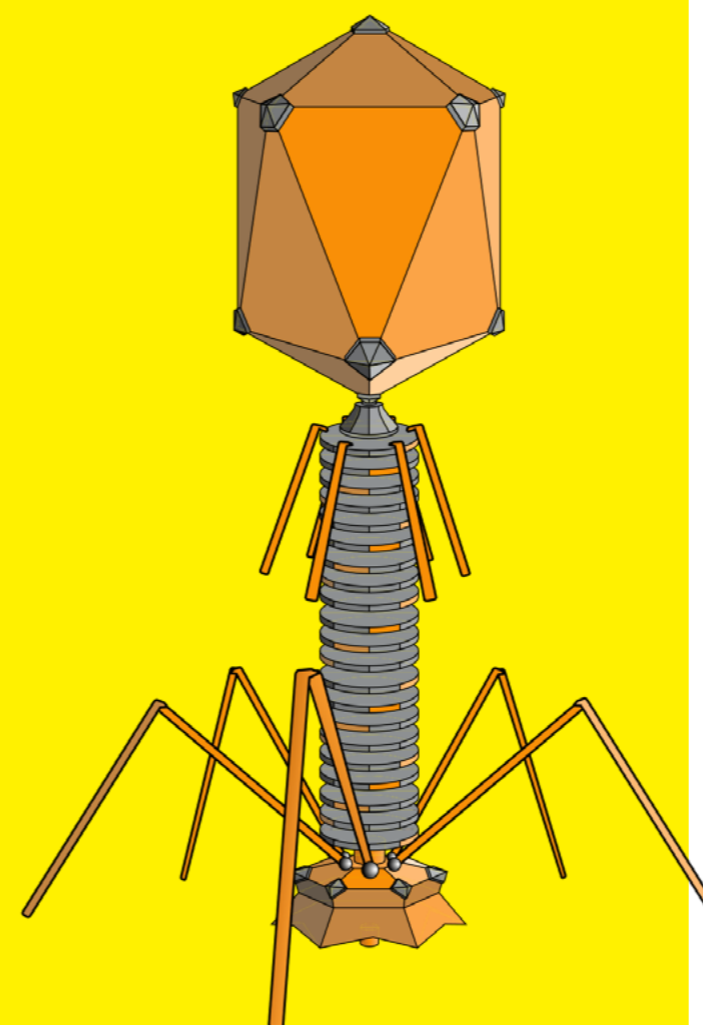
2. Lee YC, Leu SJ, Hu CJ, Shih NY, Huang IJ, Wu HH, Hsieh WS, Chiang BL, WT Chiu WT, and Yang YY*. (2007) Chicken single-chain variable fragments against the SARS-CoV spike protein. *Journal of Virological Methods* 146:104-111.

In 2009, Taiwan’s CDC was looking for a way to deal with another health danger: snakebites. Taiwan has six major species of venomous snakes that account for over a thousand bites per year. Effective antivenin treatments are available, but the traditional anti-venom antibody production system using horses is expensive, inconvenient, and risks dangerous side effects.

After having produced avian antibodies using phage display during his SARS research, Dr. Yang suggested using the chickens for their ease of care, low space requirements, and because chicken-derived antibodies may not be as easily rejected by the mammalian immune system. The plan was successful, and the team’s experience in phage technology was able to successfully develop mono and polyclonal antibodies for antivenin. Since 2009, Dr. Yang and his team have successfully used phage display to develop antivenin for all 6 species of venomous snake in Taiwan – results have already been published in several papers.^{[3], [4]}

3. Lee CH, Lee YC, Lee YL, Leu SJ, Lin LT, Chen CC, Chiang JR, Mwale PF, Tsai BY, Hung CS, Yang YY*. (2017) Single Chain Antibody Fragment against Venom from the Snake *Daboia russelii formosensis*. *Toxins (Basel)*. Oct 27; 9(11).

4. Lee CH, Leu SJ, Lee YC, Lee YL, Liu CI, Lin LT, Mwale PF, Chiang JR, Tsai BY, Chen CC, Hung CS, Yang YY*. (2018) Characterization of Chicken-Derived Single Chain Antibody Fragments against Venom of *Naja Naja Atra*. *Toxins (Basel)*. Sep 21; 10(10).




The Future of Phage Display at TMU

But while developing antivenin has been a successful implementation of the technology, it only shows partially the power of phage display to produce specific antibodies. Besides antivenin and treatments for infectious diseases,^{[5], [6]} developing antibodies for cancer-specific biomarkers has more wide-ranging clinical application. In addition, the TMU antibody group is going to apply this technique to generate specific antibodies against tumor-associated antigen in domestic llama this year. says Dr. Yang.



Phage display technology is challenging to learn, but there are many opportunities in the biotech industry for those with the lab skills needed to develop and produce valuable antibodies for diagnostic and therapeutic applications. Providing our professional knowledge and advice to TMU colleagues for their research and, perhaps prepping students for job opportunities in the growing field of antibody research for therapy and diagnosis, is a major mission of our core facility. A lot of world biotech companies are interested in this technique ... I would like to pass this technique to faculties and students who are interested in the antibody research and industry. It’s a very hot area.”

Hot indeed. At present, five of the top ten best selling drugs in 2018 are antibodies for treating cancer or autoimmune diseases, including Humira (sales over 20 billion), Herceptin (sales over 7 billion) and Avastin (US sales over 7 billion).

And as for students like Dr. Yang’s PhD now working as a post-doc fellow. “They’ll have no problem to find a job in a good biotech company.” 

5. Mwale PF, Lee CH, Lin LT, Leu SJ, Huang YJ, Chiang LC, Mao YC, Yang YY*. (2020) Expression, Purification, and Characterization of Anti-Zika virus Envelope Protein: Polyclonal and Chicken-Derived Single Chain Variable Fragment Antibodies. *Int. J. Mol. Sci.* Jan. 21, 492.

6. Leu SJ, Lee YC, Lee CH, Liao PY, Chiang CW, Yang CM, Su CH, Ou TY, Liu KJ, Lo HJ, Tsai BY and Yang YY*. (2020) Generation and Characterization of Single Chain Variable Fragment against Alpha-Enolase of *Candida albicans*. *Int. J. Mol. Sci.* April. 21 (accepted).

Dr. Yi-Yuan Yang

Deputy Dean and Professor, School of Medical Laboratory Sciences and Biotechnology, College of Medical Sciences, Taipei Medical University

Saving Kids with Stem Cells

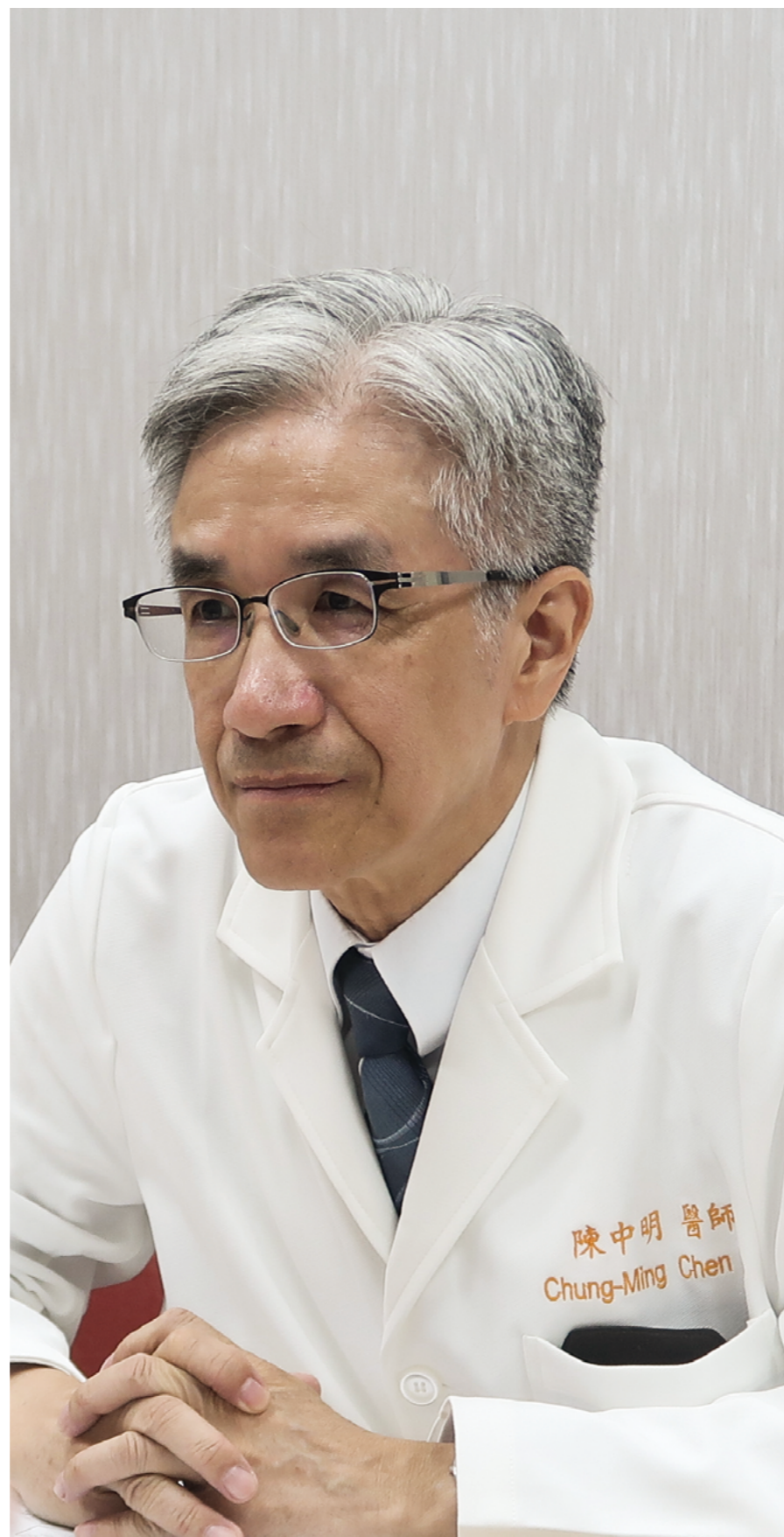
Preterm birth is the leading cause of death for newborns. Although survival rates have improved for babies born before the 37th week, their immature lungs remain vulnerable to inflammation, infection, and sepsis. Standard procedures using steroids and mechanical ventilation can cause further oxidative stress and lead to bronchopulmonary dysplasia (BPD). Children with BPD may suffer from recurrent lung infection and require extended stays in the ICU, and often see decreased lung function and higher susceptibility to infection as they age.

As treatments for prematurely born infants have advanced, so has the incidence of BPD, a problem Director of the TMU Hospital's Department of Pediatrics Dr. Chun-Ming Chen has watched grow in a career spanning close to 35 years. But standard treatments, according to Dr. Chen, are lacking in effectiveness.

"Old treatments," including vitamin A, erythromycin, and steroids, "aren't supported by evidence," says Dr. Chen, who has his sights set on a novel and promising treatment. Harvested from umbilical cords, mesenchymal stromal cells (MSCs) are stem cells able to proliferate and differentiate into a variety of tissue. Importantly for infants with BPD, cells administered directly through an endotracheal tube have the ability to enhance lung development and reduce pulmonary hypertension^[1].

Dr. Chen first pursued an interest in stem cells as a Neonatology Research Fellow at Harbor-UCLA's School of Medicine. After a year studying stem cells in sheep, Dr. Chen returned to TMU and began experimenting on rats. Dr. Chen has been working with stem cells ever since, and is the only researcher in Taiwan working with stem cells in a rat model of BPD.

1. Chen C., Lin W., Huang L., Chou H. Human mesenchymal stem cells ameliorate experimental pulmonary hypertension induced by maternal inflammation and neonatal hyperoxia in rats. *Oncotarget*. 2017; 8: 82366-82375. Retrieved from <https://doi.org/10.18632/oncotarget.19388>



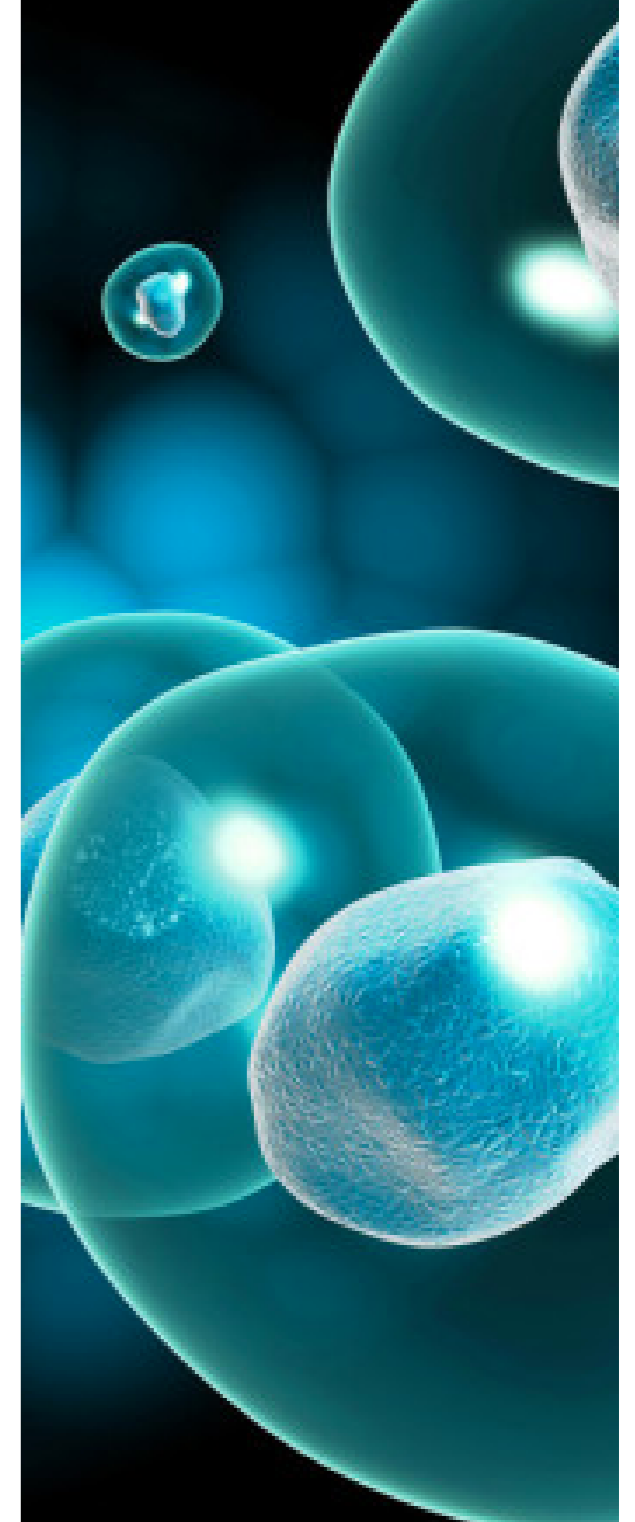
With lung development closely matching that of humans (and whose space requirements are much lower than sheep), rats were a clear choice for modeling lung disease in humans. In studies he's published over the past several years, Dr. Chen has used his model to show the efficacy of MSCs at reducing lung inflammation and attenuating BDP^[2]. He's also worked out the MSCs' protein signaling pathways on lung tissue in rats, but the most important goal "... is the use in the human body. The future study should focus on dosage and time of administration."

Being a pioneer of new - and sometimes poorly understood - treatments can bring challenges, says Dr. Chen. Despite a similar treatment from a Korean team showing no adverse effects at two-year follow-up (the American team has yet to publish their results), regulatory hurdles can slow the process of recruiting subjects. Until there is more data, the TFDA (Taiwan Food and Drug Administration) currently requires a full report one year after treatment, and only allows one patient to be treated at a time. On top of that, treatment approval can be delayed until after patients are extubated, at which point MSCs can only be administered intravenously.

"I think animal studies are already enough for beginning human studies. But it's hard for clinicians, it's tough to meet the requirements of the TFDA," says Dr. Chen. While a conservative pace focusing on safety may be understandable, he looks forward to more easily enrolling the patients at the time they'll see the greatest benefits from stem cell treatment.

Students interested in becoming stem cell pioneers in a rapidly developing field can get involved through the CCTRM's (Center for Cell Therapy and Regeneration Medicine) international PhD program. Besides undertaking pioneering research with experienced researchers, gaining access to CCTRM's world-class animal facilities and the support of TMU's Office of Business Development, international PhD students build a network of connections with the international medical community. And for local students and faculty the chance to work in a culturally diverse environment for academic and clinical advancement is "a great thing for our colleagues," says Dr. Chen. 

2. Chou, HC, Li, YT & Chen, CM 2016, 'Human mesenchymal stem cells attenuate experimental bronchopulmonary dysplasia induced by perinatal inflammation and hyperoxia', *American Journal of Translational Research*, vol. 8, no. 2, pp. 342-353.



Dr. Chung-Ming Chen

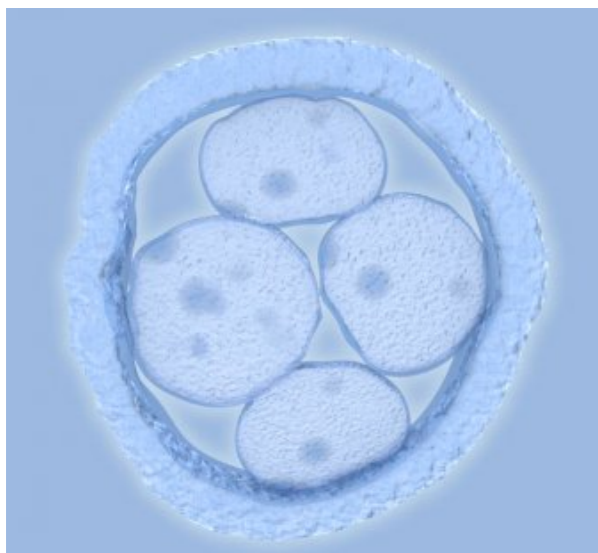
Director and Professor, Department of Pediatrics,
Taipei Medical University

Seaweeds, stem cell therapy, and health of liver disease patients

From a medical family, versed in medical traditions from the East and West, and with interests in both basic and clinical research, Dr. Ming-Shun Wu draws on a broad range of knowledge in medical research and practical expertise for the good of his patients.

“I followed him into the mountains to take some herbal medicines. He also taught me to palpate pulse, to do acupuncture.”

Dr. Ming-Shun Wu began his interest in medicine from childhood. When accompanying his grandfather, he learned how to use Chinese herbs and traditional techniques. He later brought his interest in healing to TMU, where he earned his MD and PhD in clinical medicine, filed licenses in both Chinese and Western medicine, and has served at Wanfang Hospital for the past 26 years. Director of TMU’s Department of Gastroenterology since 2015, he also teaches at the TMU Center for Cell Therapy and Regeneration Medicine. His eclectic background is reflected in a broad range of research interests that span Traditional Chinese Medicine (TCM) diagnosis and treatments, clinical research on components of herbal remedies, and stem cell therapy for cancer treatment.



Fucoidan, Fucoxanthin, and Fatty Liver Disease

“The function of seaweed in Chinese medicine is to lose weight and reduce tumors.”

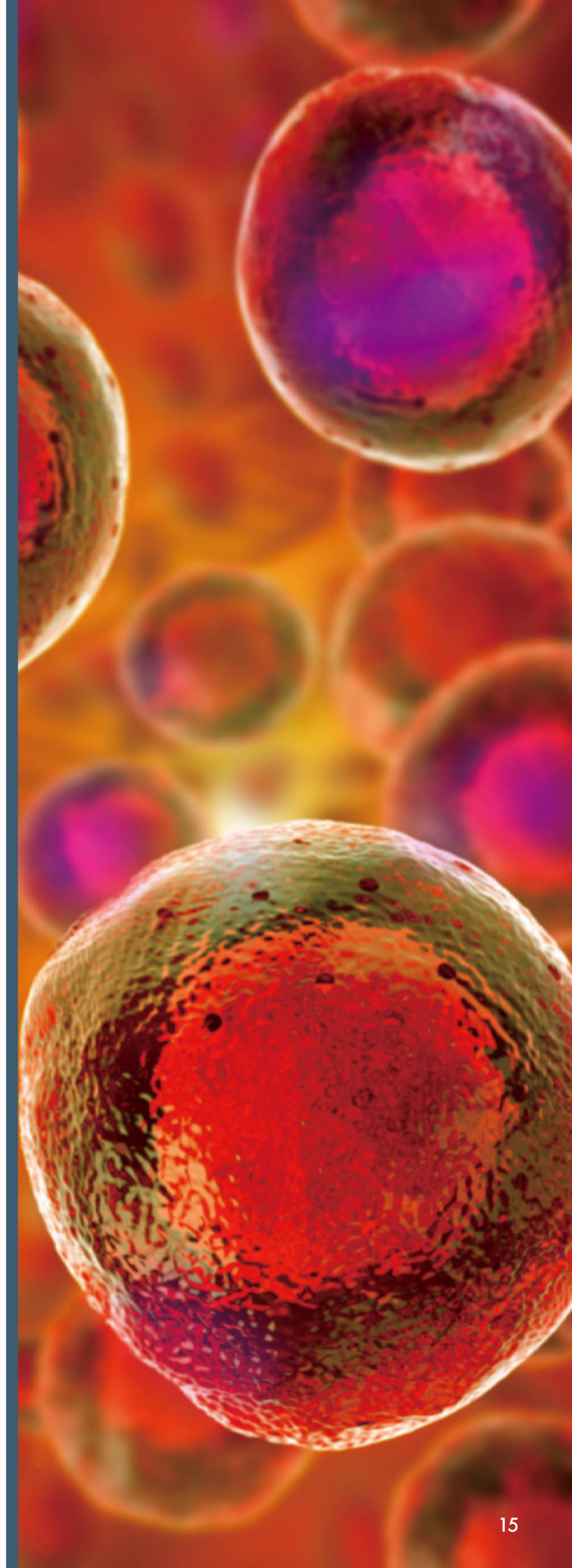
Brown seaweed has been used in traditional herbal medicine for weight loss and tumor reduction. More recently, studies have shown beneficial effects stemming from two of the plant’s compounds; fucoidan fights viruses, inflammation, and tumors, while fucoxanthin acts as a potent antioxidant that can modulate inflammation and cancer.

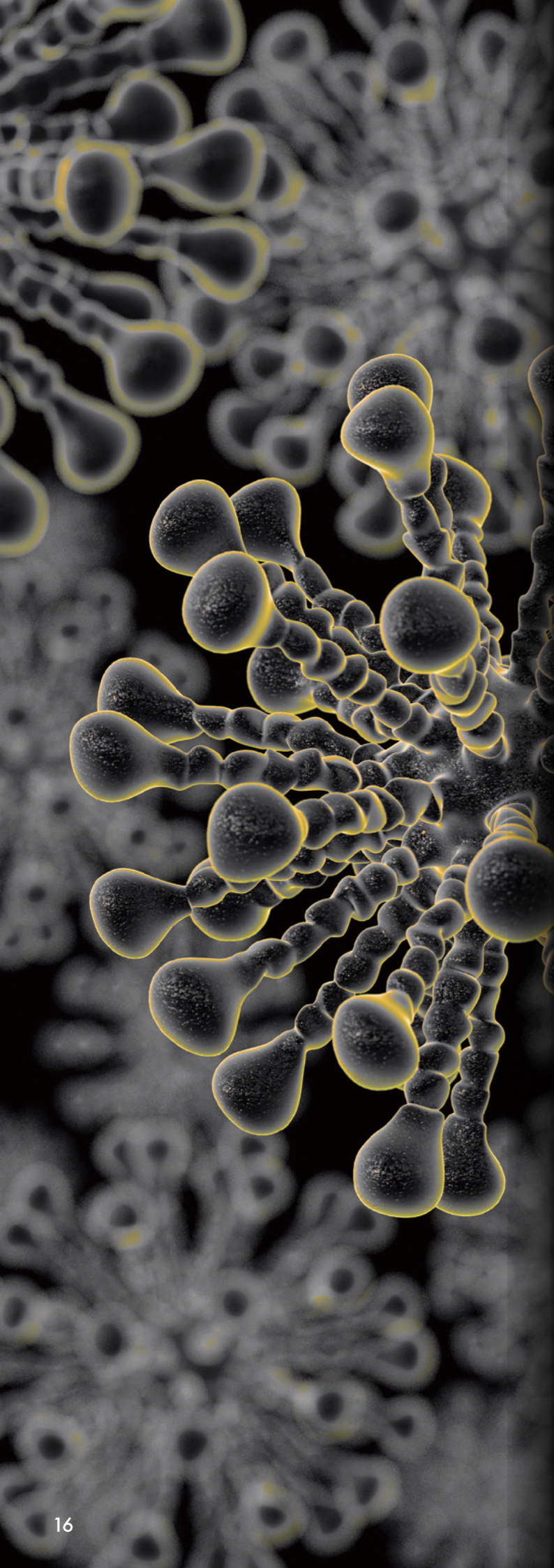
Although eating one would be healthy, you probably can’t get all the benefits of fucoidan and fucoxanthin from a seaweed salad. According to Dr. Wu, the concentrations are too low, and absorption may not be ideal. These problems are something that HiQ Marine Biotech wants to address with a patented brown seaweed supplement.

The company contacted TMU’s Office of Business Development to conduct a study of their product, and a background in Western and Chinese medicine, clinical and research expertise, and access to patients at Wanfang Hospital placed Dr. Wu perfectly to look into HiQ Marine Biotech’s product.

In a double-blind study^[1] of sufferers of non-alcoholic fatty liver disease, patients were given a regimen of brown seaweed supplement or placebo. Evaluated at one and three months, patients in the treatment group showed increasing improvements in blood markers for liver. Physical changes to their livers took a bit more time, but decreased liver fattiness was seen by month six.


According to Dr. Wu, NAFLD (Non-Alcoholic Fatty Liver Disease) may potentially lead to problems such as cirrhosis and cancer, and there is little certainty regarding existing pharmacological interventions. So for patients who are less able to make lifestyle changes because of disability supplementation looks like a good option. And because chronic inflammation of the liver can induce cancer, further investigations into how the underlying mechanisms of fucoidan and fucoxanthin reduce inflammation are planned.





New Opportunities in Stem Cell Therapy

As governmental regulations loosen, Dr. Wu also plans to work with companies to develop stem cell products to treat patients with liver cirrhosis and stage 4 cancer. Dr. Wu is hopeful about this newly opening avenue of research. In a yet to be published case study, he reports preliminary success using stem cells to extend the life of a stage 4 cancer patient by 11 months.

From cutting edge stem cell treatments to basic cancer research to improving health outcomes through TCM-informed nutritional supplements, Dr. Ming-Shun Wu's work embodies a most effective melding of Eastern and Western traditions. You can hear his perspective first-hand in TMU's International Master's or PhD Program in Cell Therapy and Regeneration Medicine. 



Dr. Ming-Shun Wu

Director, Division of Gastroenterology, Department of Internal Medicine, Wan Fang Hospital
Assistant professor, School of Medicine, Taipei Medical University



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TAIPEI MEDICAL UNIVERSITY

A Step Beyond CAR-T: Culturing Bispecific Antibodies

T-cells are the most powerful cells of the body's immune system. They are responsible for eliminating invaders or abnormal cells, but aren't very good at recognizing cancer on their own. At the cutting edge of immune antibody treatments, CAR-T therapies have extended the lives of thousands of patients by modifying the body's own immune cells to attack and destroy cancer. CAR-T treatments indeed look promising; products like Kymriah and Yescarta have been a game-changer for treating leukemia and b-cell lymphoma, and globally there are presently close to 350 ongoing CAR-T clinical trials.

In CAR-T therapy, T-cells are harvested from a patient or donor's blood, given new genes using a retrovirus so they can grow a specific receptor (a chimeric antigen receptor, or CAR), and are reintroduced into the patient - now able to attack a specific target like cancer. But engineering CAR-T treatments is a complicated and time-consuming process; it is expensive and not without risk.

According to Dr. Kuo- Hsiang Chuang, besides costing upwards of half-a-million dollars per treatment and carrying the risk of causing deadly cytokine release syndrome, CAR-T treatments themselves can become carcinogenic if the CAR gene is unintentionally introduced into cancer cells - effectively conferring resistance to a patient's cancer. On top of that, the process takes around 30 days, time that a cancer patient may not have.

With these problems with CAR-T therapy in mind, Dr. Chuang developed a novel method of culturing antibodies that he says is faster, cheaper, and safer than traditional CAR-T methods. Dr. Chuang's strategy is to use bi-specific

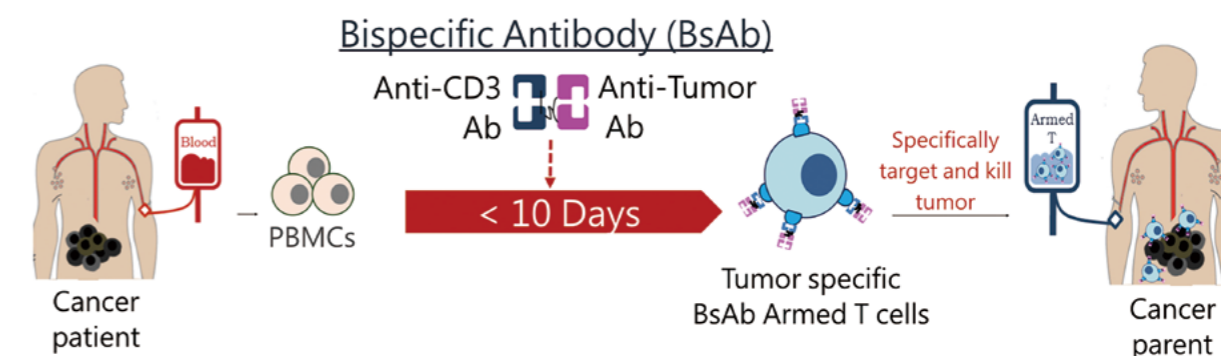


antibodies (BsAbs) that can recognize two antigens at the same time.


Specific BsAb treatments can be built a bit "like Lego", says Dr. Chuang. "We can reassemble the protein or antibody depending on our needs. One arm [of the BsAb] can target the tumor, and the other arm can target something to help you kill the tumor effectively."

As with CAR-T, blood cells were first harvested from patients. Then in Dr. Chuang's one-step process, BsAbs that bind to human T cell's CD3 receptor and an anti-PSMA (prostate specific membrane antigen) agent were added to the culture medium. These BsAbs were able to differentiate and expand human CD3 positive T cells, and when introduced into mice, accumulated at tumor sites, leading to tumor cell death for two types of cancer.

Because Dr. Chuang's BsAb culturing method does not require retro-virus based gene transfection, it will not unintentionally confer treatment resistance to cancer cell, and because it does not require a laborious incubation process, it is much cheaper and faster. Instead of a 30-day wait, a patient-specific treatment could be ready in less than 10.



With his study showing promise for targeting EGFR (epidermal growth factor receptor) and PSAM positive cancers, Dr. Chuang and team are looking at using different particular antibody building blocks to precisely target other cancers or autoimmune diseases like rheumatoid arthritis and type 1 diabetes.

The future of Dr. Chuang's non-viral bispecific antibody culture method looks bright. With help in part from TMU's Office of Business Development in providing support services for financing, facilitating tech transfers, academia-industry liaising, and making patent applications, the team have already been approached for research collaborations and development of new bispecific antibody therapies with industry players. 

Dr. Kuo-Hsiang Chuang

Associate Professor, Graduate Institute of Pharmacognosy,
Taipei Medical University



After building expertise in protein and antibody engineering at Kaoshiung Medical University under Dr. Tian-Li Cheng, Dr. Kuo-Hsiang Chuang jumped at the opportunity to join the TMU family in 2012 at the Graduate Institute of Pharmacognosy. Dr. Chuang says that mentorship under Dr. Cheng was invaluable, both for learning techniques to develop therapeutic bi-specific antibodies and for developing a professional and productive laboratory culture.

"I learned a lot about the scientific method and good attitude from my teacher. [Dr. Cheng] taught us that you need to have good friendships with your colleagues, and smart experimental methods," said Dr. Chuang, "And work hard. Work very hard!"

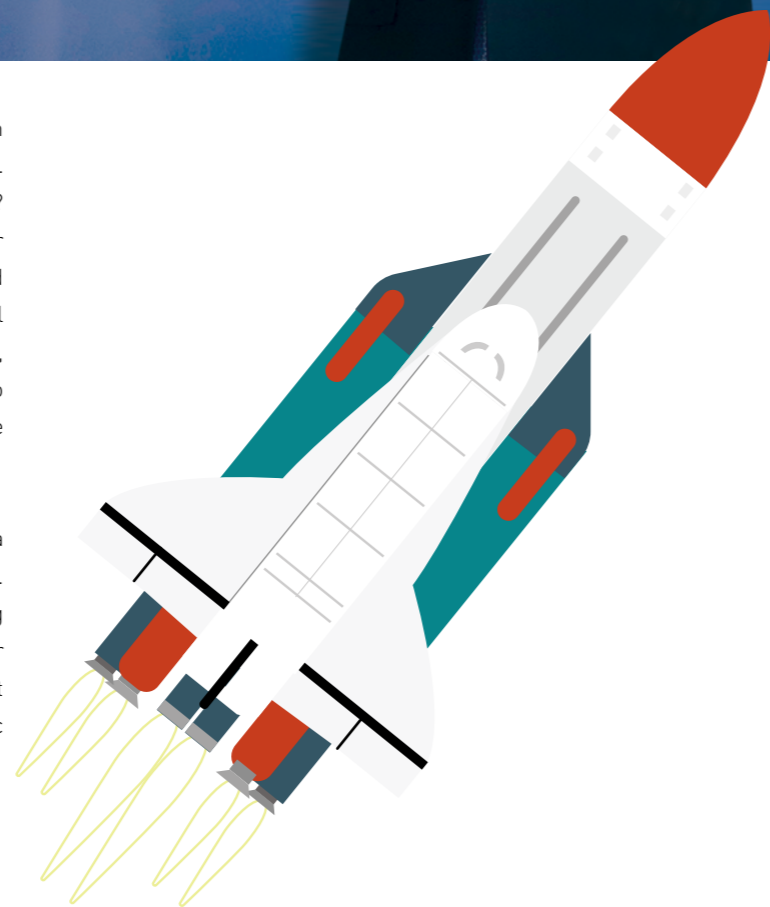
AIR Academy of International Research

Academy of International Research – Empowering You to Achieve Higher!



Entering the world of international academic research can be an exciting but daunting prospect for the uninitiated. Questions like, "Where should I go? Who can I work with? How can I get funding?" might be intimidating, but for students and researchers at TMU, answers can be found through the newly inaugurated Academy of International Research. At the AIR kickoff event held October 3rd, VIPs, staff and alumni gathered to show TMU's commitment to supporting international research collaborations and share their experiences.

Back in the 80's, entering the international research arena could be challenging, according to speakers at the kickoff. Finding the right research partner wasn't easy, and budding researchers were often left to figure things out on their own. Access to information has increased since then, but finding detailed specifics and accessing personal academic networks can still be tough to do alone.



That was the opportunity identified by TMU leadership; an organizational space to provide researchers with the assistance and information needed to raise their professional profiles. And so with TMU's significant emphasis on international research collaborations and administrative backing at the highest levels, AIR was born.

AIR's mission is to create an international research friendly environment by helping to develop collaborative

international partners and assist with any questions researchers may have. Once members have an idea where they would like to go, they will be invited to bring research proposals to a mentor-led "think-tank" for a checkup and suggestions for improvement before submission. AIR staff can also assist with applications for funding such as TMU and Ministry of Science and Technology (MOST) grants.

The kind of experience to be gained from international


research partnerships. Spearheaded by Office of Global Engagement staff who provide comprehensive consultation and mentorship services backed by consultative policy guidelines, AIR will help raise the international profile of both researchers and the University.

Information available through AIR will include guidelines for international collaboration, FAQs for funding application procedures, and access to an interactive membership database. AIR's consultation services will facilitate communication with partnering institutions and assist with their specific application procedures. More information will be available through AIR's upcoming four-part lecture series covering international branding, partnerships, and perspectives from key insiders.

AIR's member database will put researchers in contact with a pool of experienced mentors who can recommend

collaborations is valuable, according to kickoff attendee Dr. Chi-Wei Peng, who was there gathering information for colleagues at the School of Biomedical Engineering. Like most researchers, Dr. Peng is always on the lookout for more access to funds, and in his experience "international partners are welcoming," he said.

In addition to being an easily accessible repository of experience and information and a base for professional networking, helping with funding is a big part of what AIR can do. "We want to create a researcher-initiated cohort that can work together to find spaces in the crowded funding area," said Dawn Chen, OGE Vice Dean.

So if you're thinking about taking your research to the next level through international partnerships and collaborations, keep an eye on the AIR website for upcoming activities or come chat with staff at the OGE. 

We **T**eam up with global partners to bring diversity to our

delivery. Our strong **M**otivation to improve the health

of our communities keeps us going forward in **U**nity.

TMU Spotlight brings impressive outcomes from our partnership collaboration, research excellence, talent cultivation initiatives, and the University's efforts to make a positive social impact.

