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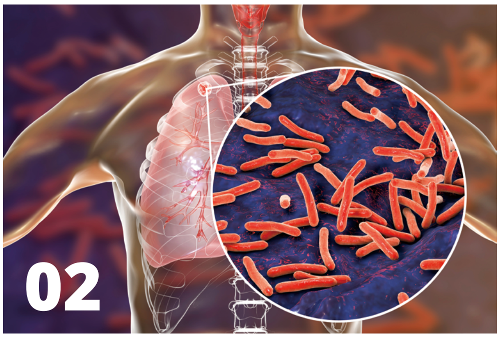
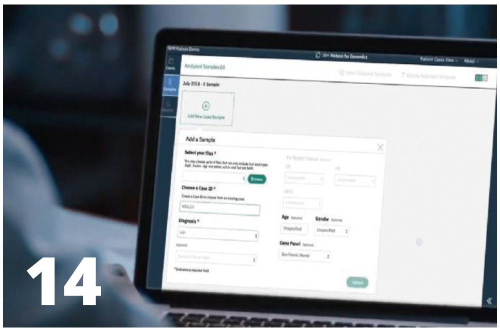
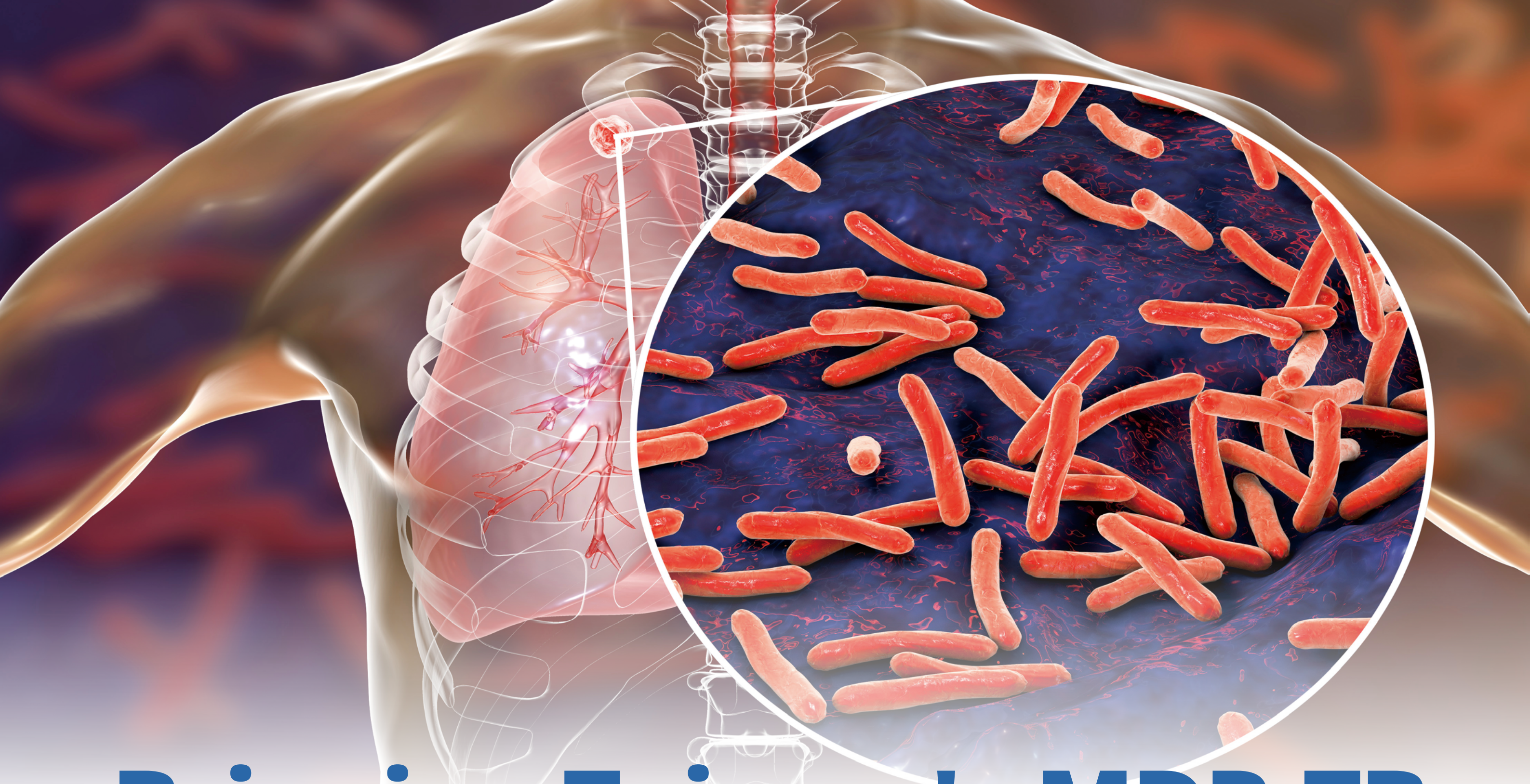






Bringing Taiwan's MDR-TB treatment experience to the world

Dr. Chen-Yuan Chiang's original interest lay in psychiatry. But as he ran into difficulties reconciling Western theories with an Eastern culture, he decided to move to a combination of internal medicine and public health. After graduating from Kaohsiung Medical University, he went on to receive a Master of Public Health at the University of California, Berkeley in 2003, and a Doctor Philosophiae at the University of Bergen, Norway in 2012.

Now Dr. Chiang spends about half of his time in Taiwan and half globetrotting as a national level advisor for tuberculosis related public health programs through The Union, where he has been working since 2003 when he was invited to join for his expertise in TB and lung disease. In this capacity Dr. Chiang often operates at the national policy-making level, being invited by governments and national or country level advisors to provide guidance on public health program implementation.

In 2007 Dr. Chiang was invited to establish a department of lung health and non-communicable disease in The Union. Through this department he implemented pilot projects to deal with the management, diagnosis, and care of patients living with asthma in mainland China, Sudan, Benin, and El Salvador. Although effective asthma treatments do exist, patients in resource-limited settings may not have access to care, while asthma medicines that are available may not be affordable or quality assured.

Management of MDR-TB: A Holistic Approach

Treatment success for TB in mainland China sat around 50% under the global fund project. However, increasing out of pocket expenses seems to have been a major barrier in MDR-TB treatment. With a CAP-TB project seeking to address the challenge in the management of MDR-TB, Dr. Chiang was invited to look into the components of treatment processes as a technical adviser to determine how best to make a positive impact on patient care.

The CAP-TB project takes a holistic approach that looks beyond physical symptoms to include patients' family and life situations. In addition to out of pocket expenses for treatment that can mean injections and oral medications every day for 18 months, the burden of indirect costs, such as for transportation to a distant clinic, can prevent patients from completing treatment. For example, a 9-month MDR-TB regimen pilot project in the Philippines showed a promising increase in treatment success. However, the proportion of patients lost at follow-up remained substantial. According to Dr. Chiang, many MDR-TB patients end up stopping treatment or taking medications irregularly, not because of side effects or adverse reactions, but "most of the time the supporting system wasn't good enough. You can imagine, the patients they are young, they may have babies... and need to travel every day to the facility for injections and oral medicine, it doesn't work. It means that you need to take the patient's perspective to understand the difficulty."

These problems are what the CAP-TB project in Yunnan and the TREAT TB programme in the Philippines try to address. Thanks to Dr. Chiang's input, the Cap-TB project includes a patient centered support group that leverages mobile phones and the internet to provide a support services package including regular meetings with patients, a 24-hour hotline, treatment reminder calls from nurses, and even help for patients to physically get to treatment. The project aims to build a sense of community and group belonging that can support patients emotionally as well as physically, with the end goal of better treatment outcomes. In the Philippines, the TREAT TB programme took the advice of Dr. Chiang to focus on treatment interruption and to decentralize treatment services to the community.

CAP-TB in and TREAT TB successes build on Dr. Chiang's experience in working with Taiwan's successful TB programs. Working with Taiwan's CDC, Dr. Chiang was the editor-in-chief of Taiwan's Guideline for TB diagnosis and treatment. He supported the set-up and operation of the Taiwan MDR-TB Consortium's regional network of five hospitals (including TMU's Wanfang Hospital), that mobilizes CDC financial resources to give patients access to supportive treatment and care in the community. With this patient centered approach that helps patients deal with emotional and financial hardships as well as physical symptoms, Taiwan now has one of the best MDR-TB programs in the world.

Although it's still early to show treatment results, Dr. Chiang was informed that Yunnan's MDR-TB treatment program is the most successful in mainland China. "They sent an email to me to say 'We are so proud, so happy!' But there's still room for improvement. A success rate approaching 60% isn't good enough." Dr. Chiang would like to see a number closer to 80%, one that he thinks would be possible through a shortened but effective 9-month treatment regimen.

Policy-making from the Streets

The project in Yunnan is one of many that Dr. Chiang is involved with around the world. He makes regular advisory visits to Mongolia, Nepal, Vietnam, Sudan, the Philippines, Papua New Guinea, Thailand, and Laos. And his trips to Vietnam are set to increase. Just this year a Taiwan-Vietnam project has been initiated through TMU with funding from the Taiwan CDC, so more trips are planned to help bring a holistic approach to MDR-TB treatment and care to Quảng Ninh province in Vietnam.

Although much of his time is spend in policy discussion, Dr. Chiang still finds time to visit those in the trenches, where his interest in psychology comes in handy with patients who approach a doctor not necessarily for lung disease, but for cardiac symptoms, stress, or even emotional reasons. "You can understand [the patients] and know their complaints... You don't take them just like an organ, you approach them as a human being. It's quite useful"

Speaking with local clinicians is also valuable to someone with unique experience both as a clinician and in public policy. Whenever possible, Dr. Chiang takes a day out of each trip to understand doctors' impressions of how the programs created in international meeting rooms are actually implemented. "It doesn't matter what your policy says, if you cannot provide services properly then those things on paper will not work."

Back in Taiwan

Dr. Chiang still enjoys speaking with students, so he finds time to discuss cases with them when he's back at Wanfang Hospital. Students today have the freedom – and challenges - of choosing between a wide range of career paths, and they have increasing opportunities to develop an international perspective through travel. "It's important for them to be well trained and be a master of medicine or surgery or the field they are interested in. They need to really enjoy what they are doing and develop their interests. It's important for them to see the whole spectrum of what's possible."

Dr. Chen-Yuan Chiang

- Associate Professor, Department of Internal Medicine, College of Medicine

1. Nunn, A. J., Phillips, P. P. J., Meredith, S. K., Chiang, C. Y., Conradie, F., Dalai, D., ... Rusen, I. D. (2019). A trial of a shorter regimen for rifampin-resistant tuberculosis. New England Journal of Medicine, 380(13), 1201-1213. https://doi.org/10.1056/NEJMoa1811867

A precision approach to the lung cancer microenvironment

After having completed his medical degree at TMU and clinical training at Chang Gung Memorial Hospital, Dr. Kang-Yun Lee worked under Dr. Han-Ping Kuo, (now Dean of the College of Medicine at TMU). Having showed the potential for research excellence, Dr. Lee was supported by Chang Gung to pursue a PhD in thoracic medicine at the National Heart and Lung Institute at Imperial College London.

There he honed his ability under Dr. Peter Barnes (a world class lung disease researcher who has published over 1000 papers) to complete independently background study while at the same time designing rigorous scientific experiments. Under Professor Barnes, Dr. Lee developed his interest in asthma and airways diseases, first focusing on the inflammatory mechanisms underlying chronic inflammatory airway diseases.

After earning his PhD in three years, Dr. Lee returned to Taiwan working on translational research in airways diseases. Some of Dr. Lee's recent research looks at the relationship between COPD (chronic obstructive pulmonary disease) and air pollution, including a collaborative effort between TMU and the Chinese University of Hong Kong. In this study, air samples (complete with pollution) were taken from different cities in China. These samples were then injected into the tracheas of unfortunate mice, who were monitored for changes to their lung tissue. While mice exposed to air samples from the cities with lower levels of pollution remained relatively healthy, mice exposed to samples with the highest levels of pollution, including samples from Beijing did much worse. The signs of serious COPD in the high-pollution mice helped Dr. Lee and his team show a clear link between air pollution and COPD.

Lung Cancer's Microenvironment

While the environment outside can have a big impact on lung health, Dr. Lee is also looking at how things happening at much smaller scales affect lung health, specifically in the fight against lung cancer.

A wide array of different cells, including macrophages, stroma cells, fibroblasts, and other inflammatory and immune cells can affect cancer growth and spread throughout the body. All these cells and the material secreted from them, make up the microenvironment. Endothelial cells are particularly important because they allow tumor angiogenesis to occur: the building of blood vessels that feed growing tumors.

Tumor cells themselves tend to respond well to treatments such as chemotherapy. But simply killing off cancerous cells isn't the entire picture: "In the lab you can easily kill the cancer cells if you grow the cells alone, but if you put the cells with others, co-culture tumor cells with the microenvironment cells, usually you'll find the tumor cells become very resistant to treatment."

Dr. Kang-Yun Lee

- Professor, Department of Internal Medicine, College of Medicine
- Dean, Office of Human Research
- Vice Director, Research Center of Thoracic Medicine

Macrophages, for example, can kill bacteria, viruses, and even cancer cells. But as a tumor grows, it manages to change the microenvironment; changing the "character" of macrophages so that they are no longer able to kill cancer cells. In fact, classically activated M1 macrophages (the good, cancer killing cells) can be overtaken by cells of a different phenotype - M2 macrophages - that are not able to kill cancer, but instead produce growth factors that help protect tumor cells from chemo or targeted therapies, partly by assisting the formation of blood vessels that help provide tumors with nutrients.

A possible strategy against this that is being investigated by Dr. Lee is to reduce the formation of M2 macrophages. In patients with lung cancer, monocytes in the blood are abnormal, and can transform into MDSCs (myeloid-derived suppressor cells) that when exposed to a tumor microenvironment transform into M2 macrophages. Using monoclonal antibodies like bevacizumab can reduce the amount of VEGF – vascular endothelial growth factor - needed for tumors to grow new blood vessels with M2 macrophages.

But as Dr. Lee is finding, this effect depends on the specific tumor subtype; patients with EGFR mutant tumors are likely to have a good response to therapy. In these patients, the use of bevacizumab together with chemotherapy could have a progression free survival time 50% longer than those without – a finding recently published by Dr. Lee in the prestigious Journal of Thoracic Oncology[1].

The combo-treatment strategy tends to be effective for a time, but after months or years tumors can morph into a form that can escape the combination therapy. Dr. Lee is now aiming to identify biomarkers through immune-phenotyping – an "immunogram" that would allow more effective combo-treatments tailored to each patient's changing tumor microenvironment. And new possibilities are on the horizon. Dr. Lee and his team are now looking into treatments targeting platelet derived growth factor and natural killer cells. Knowing the microenvironment is key: "We need precision medicine. That means we need to measure everything, make everything clear and pick the [treatment] which might get the effect."

1. Feng, P-H., Chen, K-Y., Huang, Y-C., Luo, C-S., Wu, S. M., Chen, T-T., ... Lee, K-Y. (2018). Bevacizumab Reduces S100A9 MDSC Linked to Intracranial Control in Patients with EGFR Mutant Lung Adenocarcinoma. Journal of Thoracic Oncology. https://doi.org/10.1016/j.jtho.2018.03.032

CRISPR at TMU: A core facility forges crosstalk of research teams

Advances in technology over the past several years have brought an ancient bacterial immune defense system into the laboratory. With CRISPR's simplicity and power now giving scientists the ability to precisely edit a cell's genome, its potential applications abound for uses in medical research and therapy. Dr Hsing-Jian Kung shares with Spotlight how is this technology being brought to TMU.

CRISPR-Cas9

Dr. Kung likens CRISPR to a pair of GPS guided scissors. "You can think about our genome like a string of pearls. If a pearl is defective, you need to take it out and replace it. Now let's say there are billions of pearls there. There's this one defect and you want to replace it. It's a tremendous problem because you can't find it. CRISPR is like scissors with GPS."

Although CRISPR was discovered first in 1987, it was in 2013 that discoveries by Jennifer Doudna, Emmanuel Charpentier, and Feng Zhang, brought possibilities for CRISPR's therapeutic applications to mammalian systems. The technology allows gene editing with a degree of accuracy and ease of use not found in prior systems. CRISPR technology is not without ethical concerns when it comes to application in humans. In theory it could be used to edit genetic material in germlines or embryos to create "designer babies", although recent announcement by a researcher in China who claims to have used CRISPR gene editing to create HIV resistant twins was met with international scorn.

Dr. Kung sees parallels between CRISPR and cloning technology that began in the late 1970s. Cloning was first met with hand-wringing over ethical concerns, as time went the vast majority of scientists acted with self-discipline in line with ethics recommendations. Cloning then became a major source of therapeutic medical advances. "If we did not have cloning, then we wouldn't have the progress of the last 30 years."

A TMU CRISPR Core Lab

Dr. Kung wants to see TMU at the forefront of medical research using CRISPR. He has had his eye on CRISPR developments since the technology's inception, and early on saw its importance to medical research – believing it valuable enough that early on he supported bringing the technology to TMU with his own resources and lab space. He brought in Dr. Jenny Chu, who was familiar with the technology, to begin organizing a CRISPR lab. Now their sights are set on operating

Did you know?

CRISPRs are part of the bacterial immune system. They capture DNA from invading viruses (bacteriophages) and integrate it into the bacteria's own genome so that if the virus invades again, CRISPR arrays recognize the DNA sequence, create RNA segments to bind to the foreign DNA, and cut it apart with Cas9 or similar enzymes. While bacteria use this method to destroy invading DNA, scientists in the lab are now able to use CRISPRs to edit DNA at precise locations, adding, deleting, or modifying DNA sequences.

a core facility to provide researchers at TMU access to CRISPR technology, experience, and expertise. "This is technology in my mind that every lab needs to be equipped with."

Adapting the technology to research is not a huge difficulty. The processes do not have heavy requirements for of equipment; in fact there are simple CRISPR gene editing kits available online for young students. For researchers, laboratory outsourcing services do exist, but with only around ten CRISPR facilities in Taiwan, these come with issues of both expense and access. Because of its technological and process orientation, learning CRISPR on your own can be challenging, especially with cutting edge and novel research, and the financial and time costs of failed experiments can add up.

TMU's CRISPR core lab plans to address these issues. Saving money is one thing, but more importantly is access to expert troubleshooting and experimental design advice. One local research group, for example, bought a CRISPR kit and ran into problems with their cell survival. After failing twice on their own, they approached Dr. Chu who saw they were missing a certain selection marker. With her help, the team was able to complete their work. Dr. Chu has helped nine other labs in the past year and is fast becoming TMU's go-to CRISPR expert.

Some of Dr. Kung and Dr. Chu's own work on nutritional starvation of cancer cells shows of the power of CRISPR in medical research. Currently being prepared for publication, their study shows that knocking out specific genes allows healthy cells to survive and let cancer cells starve and die, essentially reversing cancer's resistance to drug treatments.

In the future, Dr. Chu's technical knowledge and experience will be easily accessible through TMU's CRISPR core lab, giving researchers an important resource to efficiently develop experiments. Rather than having to learn from scratch or send a package out and hope for the best, "you can do troubleshooting, we can discuss with the PI back and forth. If you spend 10,000$ doing something and it may or may not work, that's awful because of the uncertainty. But if you have someone beside you, you can know the progress and say [whether] we should modify this or not. There's really no reason," says Dr. Kung, "to reinvent the wheel."

Supporting Research from the Top

The vision for TMU's CRISPR core is to serve other TMU labs in research related to health medicines and drug discovery. The CRISPR core lab is grateful for the support of President Lin of the University in encouraging faculty to utilize the facilities. This helps TMU avoid a silo mentality of isolated labs, instead allowing researchers to engage in crosstalk and idea exchanges. In the near future, research subsidies will be made available, and free classes will be offered to help familiar students with CRISPR technology and experiment design - experience that will benefit researchers' career development.

Dr. Kung and Dr. Chu are putting together a strong base of knowledge and expertise that will make cutting-edge CRISPR gene editing technology easily accessible at TMU. "This is a technology that's not pie-in-the-sky. It's something you can do at TMU practically and efficiently," said Dr. Kung.

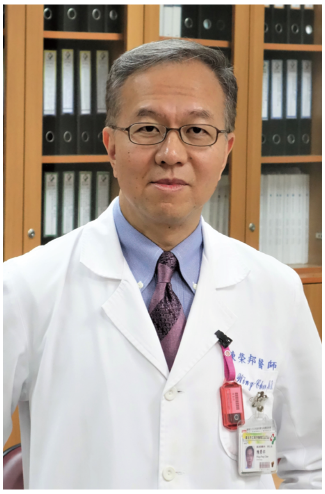
Dr. Hsing-Jien Kung

A member of Taiwan's Academia Sinica, Chair Professor of TMU's PhD. Program for Cancer Molecular Biology and Drug Discovery, and Co-PI of TMU Research Center of Cancer Translational Medicine, Dr. Hsing-Jien Kung has spent over four decades researching the molecular biology of cancer both in the United States and Taiwan. His lab pioneered research with erb/EGFR as a target gene for retroviral insertion and the identification of tyrosine profiles in prostate cancer, and now focuses on the identification of genetic and epigenetic factors contributing to cancer, including prostate cancer and Kaposi's sarcoma, and in collaborations to develop therapeutic agents that target oncogenes to enhance killing of tumor cells. His lab is also working to better understand cellular autophagy and apoptosis.

Dr. Cheng-Ying Chu

CRISPR Core Lab Director Dr. Jenny Cheng-Ying Chu has worked closely with Dr. Hsing-Jien Kung since 2008. After earning her PhD at National Taiwan University's Institute of Biomedical Studies, she held research positions at Academia Sinica's Institute of Biological Chemistry, UC Davis Medical Center, and National Tsing Hua University's Biomedical Science and Engineering Center. After moving to TMU in 2012, Dr. Chu studied cancer metabolism and tumorigenesis, drug resistance, and gene regulating and epigenetics at the TMU Research Center of Cancer Translational Medicine. Dr. Chu has been working with CRISPR/Cas9 since the early 2010s, and now heads TMU's CRISPR Core Lab.

Developing artificial intelligence for imaging analysis



Dr. Wing P. Chan

Director and Professor,
Department of Radiology,
School of Medicine,
College of Medicine,
Taipei Medical University

At a time when artificial intelligence is being hyped as a solution to a multitude of health related problems, some people are worried that tasks once done by humans may be better suited to machines – transferring health care responsibilities to computers and putting doctors out of work.

In fact, this same question was being asked 27 years ago when Dr. Wing P. Chan, now Professor and Director of Radiology at Taipei Medical University and Chief of Radiology at Wanfang Hospital, was trained as research fellow in MSK (Memorial Sloan Kettering Cancer Center) Radiology, supervised by Professor Harry K. Genant, at the University of California, San Francisco. Dr. Genant and his team were working on a machine learning classification system for vertebral compression fractures. Machine learning was at that time in its early stages, and viewed by many medical practitioners as a promising technology for interpreting medical imaging data. But the hope for new technology brought with it reservations: would this technology eventually replace doctors' eyes and brains?

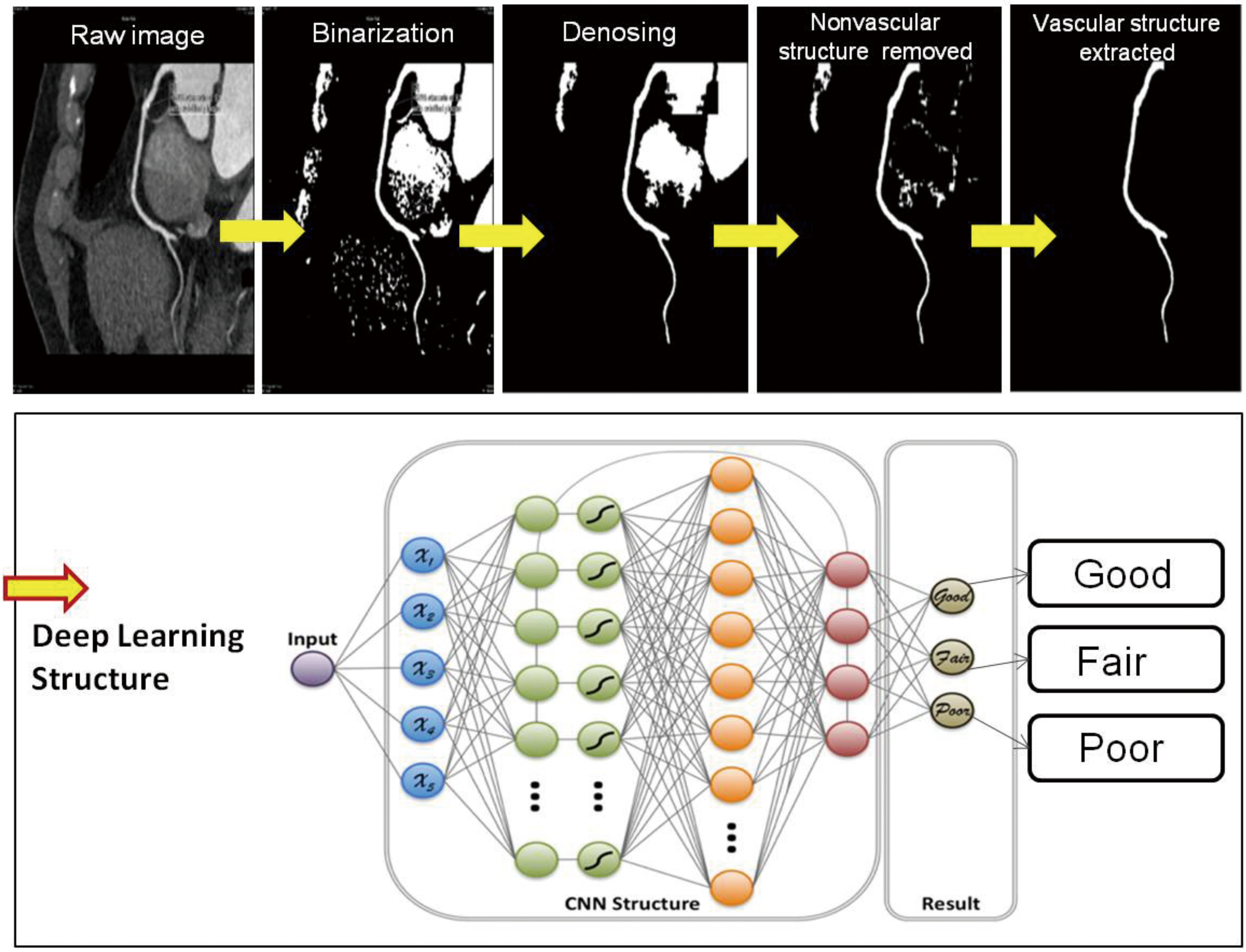
The concept of artificial intelligence began to pick up speed as computers were being developed in the 1950s. At that time, the AI concept was more like a logical process done by machine rather than an approximation of human intelligence. As the computer and medical imaging technologies advanced over the following decades, the biggest developments were in processing speed. After the development of deep learning algorithms around 2010 things began to change. Now the so-called AI systems operated like a network and began to be able to extract image features on their own, unsupervised.

When humans classify objects they see, they are able to quickly determine important features of those items. This happens in sub-second time frames, and even children can classify different objects, such as cats and dogs, in just one or two trials. According to Dr. Chan, "This is amazing. But for computers it's different. Human eyes and brains work very fast, but for machines we have to take things one by one ... and then give feedback."

Machines learning to tell the difference between a Chihuahua and a muffin is one thing, but identifying tumors or

arterial calcification is a bit more serious. This is where training done by doctors is important – but marking images for pathological irregularities is time consuming, especially when each of the minimum 200 CT scans of a 5cm tumor can be cut into 50 slices, leaving 10,000 pictures to mark. The process is further complicated by outliers or sub-clinical cases with multiple and overlapping feature sets.

Feed too many features into the system and processing could crash the computer. A brain MRI, for example, is complex, but an experienced doctor can quickly break the image down to its most important features. While it could take more than a



▲ (Upper) Automatic image feature extraction of a coronary arterial structure.
(Lower) Multi-level network analysis is performed by Convolutional Neural Network (CNN) for automated vascular structure detection.

year for a computer to process all the features in ten images, using 200 cases labeled with simple features can bring accuracy up to 85%, well within computer processing power. And more cases can increase the accuracy further.

Deep learning though convoluted neural networks (CNN) is another strategy that more closely resembles human-like intelligence. The CNN does not need images that have been labeled for features, it just needs to be told if its classifications right or wrong. This greatly speeds training and reduces the human expert's workload.

Despite the reduction in labor, deep learning is not without drawbacks. The rules the computer comes up with are hidden, and the hardware is expensive. But processing requirements can be simplified by a process called "maximized pooling", basically reducing the number of pixels in an image to increase

Despite the reduction in labor, deep learning is not without drawbacks. The rules the computer comes up with are hidden, and the hardware is expensive. But processing requirements can be simplified by a process called "maximized pooling", basically reducing the number of pixels in an image to increase contrast between different tissues. This works better on some kinds of images – neck images are relatively easier to process than whole brain scans – and giving this pre-processed data to a CNN can result in classification accuracies up to 90%. Different companies have different "black box" algorithms that can recognize pathologies from images (think IBM's Watson for example), but the ability of doctors to recognize and identify key features of medical problems and input them to the computer system is still necessary.

Dr. Chan has several AI-related projects ongoing at TMU's affiliated hospitals now. An auto-reporting system is in development to identify arterial calcification. Preliminary outcomes show promising accuracy and time savings for practitioners. Another of Dr. Chan's ideas for future AI harkens back to his days at UCSF. Now in the early stages, Dr. Chan is cooperating with industry to create an auto-detection system with three-dimensional CT scan to detect spinal compression fractures.

Although AI can speed up or even replace image analysis, the doctor's eyes and brain are still integral to medical imaging. If "the doctor doesn't have the clinical ability to point out the key feature, then the AI will not succeed" says Dr. Chan.

Data is the fuel; AI is the tool

Dr. Yu-Chuan Li

- Distinguished Professor and Dean of College of Medical Science and Technology
- Chair of Dermatology Department of Wan Fang Hospital

Though the idea of an artificial thinking machine has been around since ancient Greek writings of mechanical men, it was the early computer age that made the concept seem obtainable when the term artificial intelligence – AI – was coined in 1955 when Dr. Yu-Chuan Li was not yet born. For Dr. Li, growing up with early portrayals of artificial thinking technology in movies was fascinating, and access to early computers made it possible to begin working with AI in high school.

The Early Days

It was the early 80s, and Dr. Li was experimenting a trainable software program on a knockoff Apple 2 computer. The "Brain Maker" artificial neural network software operated with a limit of about 20 nodes, meaning that the system could only deal with 20 variables (modern AI networks can process billions). Even with early limitations, the possibilities of AI were intriguing. Could machines that deal with spreadsheets or word processing really think?

Through the rigors of medical school Dr. Li kept working with computers. In his fourth year he and a classmate created a personalized nutritionist program that operated like an early version of modern diet tracking app. As one of the earliest such trackers the program was picked up by a subsidiary of Acer, but became a victim of its own success; it showed up on a popular CD ROM of pirated software. "At that time people didn't have much idea about what's copyright, but it's an honor to be included."

As med school went on, and the difficulties of memorizing stacks and stacks of information about hundreds of diseases, Dr. Li was further motivated to pursue the possibility of actual intelligent computers. But "not just computers. I know computers, I can do programming. But I want the computer to be as intelligent at least as a medical student," he said. "I can do some deduction… but not very good with memory." So he created software for medical diagnosis so "we don't have to memorize everything."

Tapping the skills of classmates perhaps better suited to memorization, Dr. Li's early AI system produced a simple score for different symptoms and produced a list of diagnoses. But getting knowledge of many specific diseases into the computer was a struggle. "We only finished like three diseases. Writing the program is not a big problem. But getting the knowledge is very difficult."

Technology Progresses

Hearing of a cardiologist who had built a similar framework, Dr. Li travelled to the University of Salt Lake City, Utah to pursue a PhD. The cardiologist was Dr. Homer Warner, whose software could differentially diagnose 2200 diseases. At the time it was the largest disease related database in the world, but they were still struggling. Their AI was based on trying to extract knowledge from humans and represent it in a way that computers can understand – but with such a high number of diseases the team was running into computational limitations.

"When you ask the expert after he's told you something about a disease, there are ten other things that the expert didn't' tell you." The difference, says Dr. Li, is because much of a doctor's diagnostic ability comes from implicit knowledge that is difficult to put into words. It's a problem that still exists in AI today: Humans can't always express the knowledge they have, and computers can't model it appropriately. But advances would come. AI's "Age of Knowledge Representation" was soon to give way to the "Age of Machine Learning."

The paradigm shift can be illustrated by the world of computer Go. The first version of Alphabet Inc's Google Deep Mind chess playing AI was based on knowledge of Go sourced from 2500 years of books on the game. Although AlphaGo defeated top-ranked Go expert Lee Sedol four matches to one, there were criticisms that the computer was simply able to hold more examples of previous games than a human could – although it could overpower a human player through brute-force calculation, it wasn't really thinking. Designers at Deep Mind then came up with AI using a different strategy: For three nights AlphaGo played against itself, and after four million games it had become able to beat Ke Jie, the number one ranked Go player in the world.

AI in Taiwan, AI at TMU

"In medicine, you cannot let computers play with your patients," said Dr. Li. This means that medical AI still needs a database. For a database of medical information, Taiwan is sitting on a veritable gold mine with the National Health Insurance (NHI) personal health records for the island's 23 million people who see doctors an average of 15 times per year. This puts Taiwan in a "very strategic position that we could do machine learning."

In 1995 with an eye on monitoring costs and claims, the NHI instituted the computerization of all hospitals and clinics in Taiwan through the E-claim system. That same year, Dr. Li returned from Utah where he saw first-hand the value to research of an open medical data set. For religious reasons, the Mormon Church keeps extensive family records, which they opened to the University of Salt Lake City for genetic research. Researchers using the data tracked down BRCA – the first cancer-causing gene ever discovered. Finding the cause of breast cancer meant a Noble Prize, and patents worth millions, for the team. "If there was no such family database, I think it would have been another 20 years before we could discover that."

Thinking that similar research could be possible in Taiwan, Dr. Li took the post of IT Director at TMU (with a single assistant to cover three hospitals), and worked to shift the core purpose of data collection from costs and claims to electronic health records (ERH). The change was not without growing pains - like records based on Japanese kanji rather than Chinese characters causing regular system crashes - but Dr. Li persisted with system and policy upgrades that helped make leaders of TMU's affiliated hospitals integrate ERH information for research.

One of Dr. Li's projects as IT Director was the implementation of the Pharmacloud system. Designed in Canada to connect hospitals and share pharmacy data, the networking and data exchange project moved slowly until the NHI was merged with the Ministry of Health in 2013. Now with patients' pharmacy and drug data stored electronically, and with modern AI tools at their disposal, doctors and researchers are sitting on a gold mine.

Although a wealth of patient data does exist, there remains regulatory hesitancy in giving researchers fully open access. Ethical and privacy concerns sometimes put researchers in the middle of a policy balancing act between weighing patients' rights to privacy and informed consent against the scientific value of liberated data. For the time being, policymakers tend to be conservative about when providing access, but Dr. Li thinks that there may be compromises like using anonymized data, but it remains an ongoing and complex ethical debate.

Patient Safety through AESOP

Although fatal medical errors are thankfully rare, they may be increasing due to increasingly complex diseases and treatments. The problem was addressed by a research group at TMU who saw the benefits of applying AI to open data sets about doctors' prescription orders. Dr. Li's research team creased the "AI Enhanced Safety Of Prescription" system (AESOP) that reduces medical errors by helping doctors ensure they're prescribing appropriate medications.

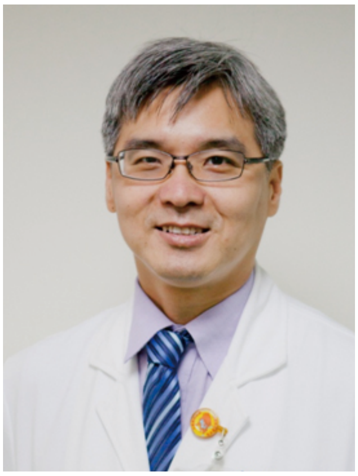
In a process that takes about 0.07 seconds, AESOP will compare a patient's diagnosis and prescription and flag any drugs that appear out of the ordinary. If a drug is flagged, the doctor has a choice of modifying the prescription, agreeing with the flag but not changing the prescription (like if the drug was prescribed for an unrelated condition) or giving a reason for keeping the prescription as-is. The system is evaluated by a three-person panel of experts with all three agreeing with AESOP in over 90% of cases.

Looking Ahead

Looking to the future, Dr. Li emphasizes the importance of "earlier medicine". Giving a patient a 50% chance of developing cancer over the next 30 years is not really actionable, but when disease takes hold it may be too late. The idea of earlier medicine is to catch things in the very early stages, after prevention, but up to a year before disease causes irreversible change. This approach does not just save lives; it increases people's years in good health.

"We're in an age where AI tools are commoditized. Big companies like Google, Amazon, Facebook, they're developing incredibly efficient and advanced AI tools," says Dr. Li. "Especially with medicine and healthcare, it's important to find the best problems that could be solved or helped by AI." Students and researchers need to understand the importance of big data, and then understand what AI can and can't do. "Find the limitation and what's the potential, and then find good problems."

AI enhances processing biosignals and TMU's investment in training AI experts



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- Associate Professor, Department of Physical Medicine and Rehabilitation
- Director, Professional Master Program in Artificial Intelligence in Medicine

Physiatrist Dr. Jiunn-Horng Kang has the calm demeanor of someone used to reassuring patients. At the same time, a somewhat mischievous smile and glasses make it seem like he is just as at home at a video game exhibition as at a patient's bedside. Between his time as a physiatrist, researcher, and associate professor, he has his assistants and students test out popular tech devices to find discrepancies between interpretations of physiological data and people's real world experiences. On his wrist is a new model smartwatch. "I wear a lot watches to see the signals I can get from different devices. Actually in our lab we have more than ten kinds of watches."

The consumer-grade devices are not altogether unlike the equipment Dr. Kang uses in the lab; a fitness tracker and electroencephalogram both measure biomedical signals from the human body that Dr. Kang wants to put to practical use for better medical outcomes.

Dr. Kang's work in biosignal processing goes back to his Master's research in EEG readings of patients with chronic pain. In the early 2000s few tools existed to help interpret the data captured in EEG recordings. Finding a solution to data processing the led Dr. Kang to pursue a PhD in biomedical engineering where he developed chaos system analysis to help understand the complexity of billions of neurons firing in the brain. "Personally, I loved the field because at that time we could do a study with just simple tools, or even a paper and pen, and do the calculations. It was an easy time!" But advances on the horizon were soon to open the field to a powerful tool for biosignal processing. After the evolution of algorithms and artificial intelligence, everything changed.

When he returned to clinical practice, Dr. Kang applied biosignals measurement and AI tools to the study and treatment of patients with chronic pain. FMRI imaging has shown that autonomic state biosignals are strongly associated to chronic pain - touch or pressure that should stimulate various brain regions instead activate pain centers. For many patients this means that sleep is often impossible without resorting to medications, and both the meds and lack of sleep have side effects that negatively impact quality of life. "It's like the brain is kidnapped by the pain," says Dr. Kang.

To bring the chronic patients' brains

back to normal function, Dr. Kang used an AI algorithm to process EEG data and determine who would respond well to non-invasive brain stimulation. Results so far are positive, and Dr. Kang is developing a home-based version of the treatment: a brain stimulating sleep cap that can be worn for ten minutes to give chronic pain sufferers a good night's sleep.

Another application that uses AI to processes biosignals is found in robot-assisted rehabilitation. TMU hospital was the first in Taiwan to incorporate the Swiss Lokomat system into rehab programs for patients with

ambulation difficulties caused by spinal cord injuries, brain damage, multiple sclerosis, cancer, or stroke. The device, that looks like a treadmill with a harness and two leg braces, uses a "bottom-up" approach; it allows repetitive movements to reshape patients' neurons, essentially helping them relearn to walk through neuroplasticity and lots of practice. The system's sensors and motors are precisely controlled by an AI algorithm that prevents patients from making uncoordinated movements or developing overuse injuries. Dr. Kang is also working on integrating "top-down" brain stimulation into the rehabilitation process.

A third area of Dr. Kang's research lies with using AI to monitor schizophrenia through micro-expressions. Micro-expressions are brief and involuntary emotion-related facial changes that are sometimes so subtle as to be barely detectable to the eye. In tests Dr. Kang's facial recognition AI was able to monitor changing micro-expressions and identify different stages of schizophrenia. The technology could prove useful to help psychiatrists identify at-risk patients or adjust medication dosages.

Powerful facial recognition brings with its privacy concerns. Dr. Kang and his team have addressed the issue by using edge computation –AI inside the camera extracts facial feature information while removing an individual's identifying details. When data is uploaded to the cloud, both important feature data and subjects' privacy are retained.

Looking to the future, Dr. Kang sees three major medical advances on the horizon. Regeneration medicine and treatment of degenerative diseases, advanced robotics in medicine, and AI integration combining software, hardware, and workflow systems to address real-world medical problems.

To prepare students for the high tech future of medicine, beginning this year, TMU is now offering a Masters' degree in AI. The program will be especially attractive for students looking to integrate medicine and engineering, but welcomes students from any discipline who are interested in biomedicine, engineering, psychology, or neuroscience. Students will take courses in programming and algorithm design while learning how to use AI to address specific, real-world problems in biomedicine.

The importance of knowing and learning practical uses and limitations of AI is clear. According to Dr. Kang (who has won three awards for excellence in teaching), "AI is important but logical thinking is much better."

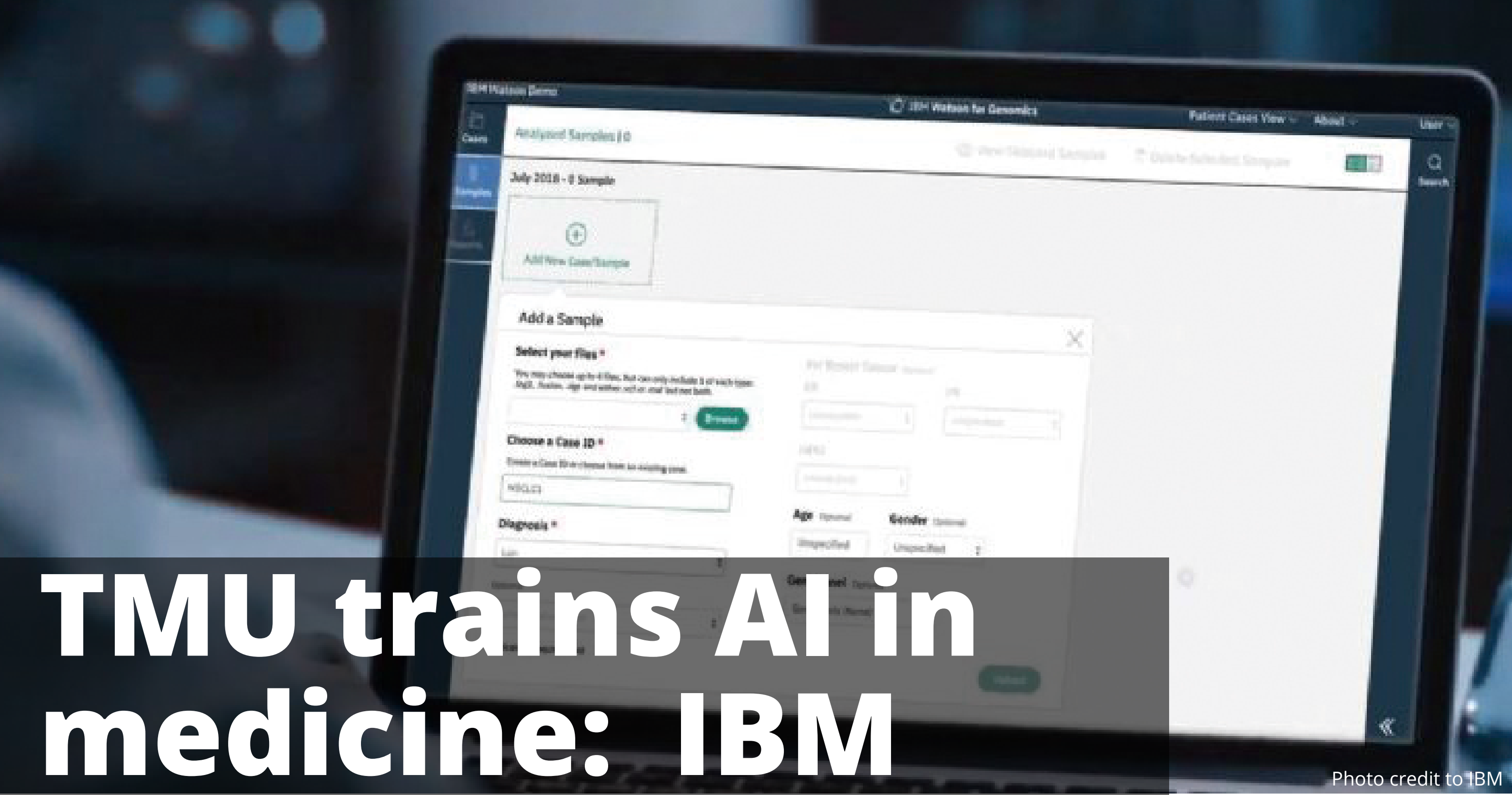


Photo credit to IBM

TMU trains AI in medicine: IBM to benefit cancer treatment

When facing a life threatening health crisis, it might sound good to have an intelligent supercomputer help inform your care, especially one that has been trained by some of the worlds' top oncologists. That is the goal for IBM's new AI based technology, which was brought to TMU's affiliated hospitals last year.

Spotlight spoke about the technology and its applications with Dr. Chun-You (Jim) Chen, radiation oncologist, self-taught programmer, and Chief Medical Information Officer at Wanfang Hospital. Dr. Chen created and continues to develop Wanfang Hospital's "One Page" patient information system, and is in charge of clinical adoption and EMR system integration of IBM's Watson for Oncology in the Taipei Cancer Center of Taipei Medical University.

What is Watson?

"It's a decision support system for the treatment of cancer," says Dr. Chen. Patient information, like pathology reports and medical images, is anonymized and uploaded through the cloud, then Watson assesses the data, evaluates medical evidence, and comes up with three detailed personal treatment regimens. Doctors can then use Watson's suggestions to make their own expert judgements based on each patient's specific circumstances. In this way Watson for Oncology works fundamentally like an expert second opinion.

Watson operates much like a physician looking for information about a case. It studies research literature, considering things like subject data, medications being tested, and experimental outcomes. Then it compares the information to the patient's situation to find the most suitable treatment options, matching data to a patient's symptoms and seeking advice when needed.

Three layers of artificial intelligence make this possible. The first layer sets the system apart from other medical AI applications. Through natural language processing Watson can "read" medical journals, textbooks, guidelines, and best practices, and build its own knowledge database. The second AI layer matches

Dr. Chun-You Chen

Medical Director,
Office of Technology
Informatics Department of
Radiology Oncology

relevant data to specific case information uploaded by doctors. And because cancer treatment must also take into account information that is not necessarily captured in research studies, a third layer of AI incorporates the experience of MSK (Memorial Sloan Kettering Cancer Center) experts who provide training data to address any data shortcomings or adjust for errors.

With the amount of media buzz surrounding Watson, it's important to keep perspective on what the system can and cannot do. "Watson is not an AI doctor," says Dr. Chen. "It's a decision support system."

The system cannot incorporate every detail or piece of subjective information that a human doctor knows about each patient's case. As with human doctors, it is also possible for the system to make errors. However, when humans and AI systems work together, the strengths are combined and shortcomings are reduced, and treatments become safer and more effective overall.

Application of artificial intelligence assisted cancer treatment at TMU

Over the past year and a half that Watson has been used in TMU's affiliated hospitals, physicians have been comfortably integrating the technology. Younger physicians adapt especially quickly, says Dr. Chen, though adding a new system can bring with it a certain level of "technological anxiety" for some. Dr. Chen thinks this could be addressed by better integration of new and existing systems into regular clinical workflows.

There are a few main scenarios for Watson's use at TMU, according to Dr. Chen. The first is when doctors are faced with difficult or rare cases that require research and consultation. Watson's massive database automatically provides a valuable evidence-based second opinion with the most up-to-date supporting research data.

Watson's second usage scenario is for reducing time and expense associated with tumor boards – meetings where 10-20 doctors from different fields build consensus for treatment options. Doctors can use Watson's detailed and up-to-date information when presenting cases, with Watson's treatment suggestions acting in essence as a third party opinion from the Memorial Sloan Kettering Cancer Center (MSK).

Watson is also becoming popular with patients, some of whom request Watson's input themselves. Doctors equipped with this "second opinion" can make related information more accessible to patients. For a system originally envisaged as a time saving technology, the process can indeed be rather time consuming – it can take up to an hour for a doctors to review details and address patients' questions about treatments, side effects, and prognoses. But this extra time is invaluable for putting patients at ease at a difficult time, says Dr. Chen. In fact, "Most of them say this is the best experience in their journey for cancer treatment."

We may already be seeing some other payoffs for bringing in AI to our clinical work to reduce sots and free up doctor's time; familiarity with the AI system could inspire physicians and researchers at TMU to develop their own AI based tools as well. In the hectic and high-pressure emergency medicine environment, the complicated triage decision making process tends happen on-the-fly and be somewhat subjective. Dr. Chen began working last year on an AI based support system for emergency room triage by using AI to monitor and quickly correlate patients' real-time vital stats with mortality rates and probable outcomes to and provide personnel with triage suggestions.

Shuang Ho designs COPD personal warning system

Shuang Ho Hospital has designed a new chronic respiratory disease warning system. This was displayed at the 2018 Taiwan Healthcare+ Expo late last year, allowing visitors a chance to try the system.

The nation's aging population, lifestyle changes and air pollution are linked to increasing rates of chronic obstructive pulmonary disease (COPD). The World Health Organization attributes 3 million deaths a year to COPD and calls it the third leading cause of death worldwide. The Ministry of Health and Welfare says around 5000 Taiwanese die from COPD each year, making it the nation's seventh-largest killer.

Thoracic medicine director Dr. Kang-Yun Lee, leader of Shuang Ho Hospital's "smart" respiratory care center, says early COPD is often misdiagnosed because its symptoms are not obvious. COPD is caused by long-term respiratory tract inflammation that is irreversible. Blockage in the tract halts air flow, leading to ineffective gaseous exchange in the lungs. Patients often seek care with symptoms of asthma, emphysema, chest pain and coughing. COPD patients face possible complications including cardiovascular disease, osteoporosis, diabetes and lung cancer. This decreases quality of life and shortens lifespans.

Thoracic medicine specialist Dr. Wen-Te Liu says artificial intelligence and novel health devices improve clinical assessment for COPD patients. This can provide earlier home-based relief for chronic respiratory diseases that were traditionally treated at large hospitals. The system promotes initial COPD screening by hospitals and clinics, providing a new care model through referrals and medical consultations.

▲ Dr. Kang-Yun Lee (right) and Dr. Wen-Te Liu (middle) use fixed and mobile air analysis devices to calculate personalized respiratory disease prediction models

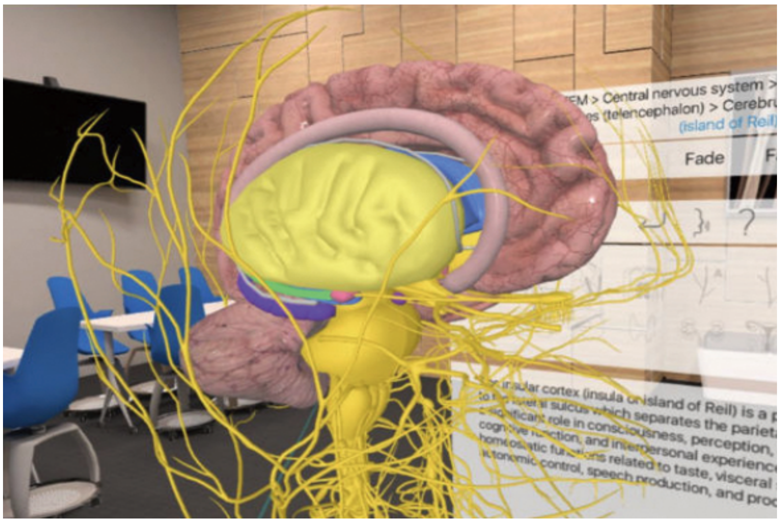
▲ Physiological information is noted by the COPD early warning system and used to generate personalized respiratory disease prediction models

The COPD warning system can record physiological information through wearable devices, while fixed and mobile air quality detection device can record environmental parameters. By comparing these results with assessments and objective questionnaires from medical institutions, data collected over a few days or weeks can be used to generate a personalized respiratory disease prediction model for tracking long-term changes to the patient's condition.

By combining technologies to provide a personal warning system, Shuang Ho Hospital offers new disease treatment approaches. This reduces barriers of distance and time between medical staff, patients and caregivers, and gives more data about the patient's condition and treatment options. This comprehensive and personlized approach improves chronic respiratory disease care.

TMU pioneers world's largest virtual reality anatomy class

In collaboration with HTC, Taipei Medical University established the world's largest virtual reality (VR) anatomy classroom in late 2018. Furnished with 10 sets of VIVE Pro (awarded 2018 VR headgear of the year) and 3D Organon VR anatomy software, this enables individual study as well as cooperative use of the same VR environment, and allows students to visualize lectures on anatomical structures in depth to better understand how bodies function.



▲ Photo credit to HTC

Anatomy and Cell Biology Director Hung-Ming Chang of the College of Medicine calls the 3D Organon VR Anatomy software students' best way to gain in-depth anatomical understanding. While cadaver dissection provides irreplaceable realism, the VR headset allows repeated examinations of various body parts unchanged by incisions and other exploratory changes that are part of cadaver study. Because the immersive 360-degree view shows tissues, bones, muscles, blood vessels, nerves and organs, students are better prepared for future clinical work.

Edward Y. Chang, HTC's health and medical division manager, says VR technology's three-dimensional visualization is a new teaching method that accelerates learning. Use of VR in medical education and clinical applications will help more students, teachers, clinical medical staff and patients in the future.

The 3D Organon VR Anatomy system's immersive learning environment increases student participation with different instructional techniques. It can support up to 300 individuals online at the same time, and can disassemble and rotate over 4000 anatomical structures in the VR environment. Besides stationary VR human body part models, the system also provides dynamic dissection models realistically presenting the extension and contraction of muscles and the beating of the heart. Even heart valve motion can be examined, giving students a perspective impossible to gain with a cadaver.

Future 3D Organon VR Anatomy improvements will complement TMU's development of more VR courses that can be applied to previews, in-class use and reviews to encourage active learning. The system will be further expanded to in-service and continuing education, the "smart medicine" EMBA and medical camps for pre-college students.

▲ Students use VR equipment to study anatomy

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