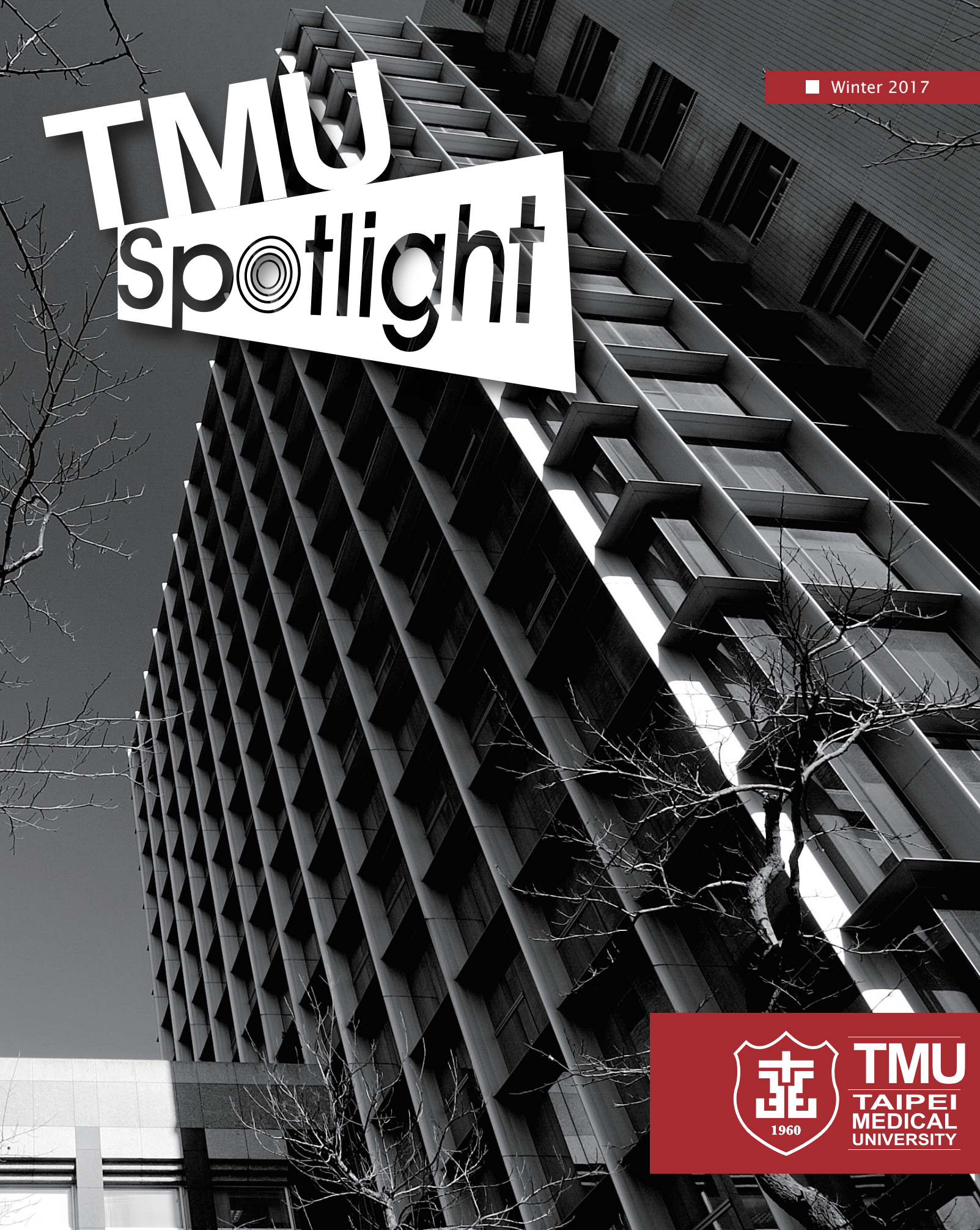
TMU Spotlight

Winter 2017



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Chief Editor: Pei-Shan Tsai
Editor: Dawn Chen
Editorial Team:
Lillian Li, Lotus Yang
Reporting: Val Crawford
Design: Cyong-Fang Jhang

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Building on strengths

Board of Trustees Chairman Chang guides TMU to focus on cancer, neuroscience & aging research

TMU Board of Trustees Chairman Wen-Chang Chang has a knack for meeting and mentoring health research leaders. He recalled old friends and former students as paged through Spotlight issues, recounting how the stories related to projects he has promoted over the years.

He noted that in his capacity as Deputy Minister of the National Science Council (now the Ministry of Science and Technology), TMU invited former U.S. National Institute on Drug Abuse chief Barry Hoffer to visit Taiwan and call on him in 2008. This led to neurotrauma research collaboration with TMU, and the resulting partnership has bloomed for almost a decade.

A year later, Prof. Chang joined the same team as a professor in the Center for Neurotrauma and Neuroregeneration, where he continues to nurture this project combining clinical studies and basic research. He manages major Ministry of Science and Technology grants and publishes a generous handful of papers each year.

Yet as Chairman of the Board of Trustees since 2014, he is at the center of day-to-day university operations. While presidents face an endless round of public appearances and speeches, Chairman Chang helps to focus resources for maximum impact in priority research areas, developing the university's strongest programs to help TMU shine on the global stage.

To say he has a long-term perspective on TMU's development is an understatement, since he took his first degree in pharmacy here when the university was still Taipei Medical College. His graduate studies were at Japan's flagship University of Tokyo. Having also taken a distinguished postdoc in a U.S. government health research institute and worked in Kentucky and London, he laughed that he'd advise students to choose the United Kingdom for speedier progress—perhaps earning their Ph.D. in three years instead of the five or six that this credential usually requires in America and Taiwan.

Selected recent honors of Chairman Wen-Chang Chang

Since 2004, Academician of Academia Sinica

2015, K.T. Lee's Science and Technology Chair, Chair Professor

2011, Member of Third World Academy of Sciences

2008-11, Deputy Minister, National Science Council

2008, Life-long Honor of National Professorship, Ministry of Education, Taiwan

2006, 16th Annual Wang Ming-Ning Award

2004, Merit NSC Research Fellow Award, Taiwan

1999, 2004, National Professorship, Ministry of Education, Taiwan

1998, Science Academy Award, Ministry of Education, Taiwan

1997-2002, Distinguished Scientist, specially contracted with National Science Council, Taiwan

From Tokyo to Baltimore

After his studies he moved to the U.S. National Institutes of Health (NIH), which in 1960 started an institute on aging research in Baltimore. That facility has since been absorbed by Johns Hopkins University, but for decades it was America's primary gerontological research center. Around 1962 this NIH program began a longitudinal heart study that helped start a global cardiac research boom as well as the first serious scientific research into human aging.

Chairman Chang calls his 30 months in Baltimore the starting point of his enduring research interests. He returned to Japan to conduct research for Tokyo's city government, which saw the demographic tsunami of a rapidly aging society approaching as families grew smaller.

"In the 1960s and '70s, both countries [i.e. USA and Japan] began paying attention to the aging problem," Chairman Chang said. "now our society recognizes this as a medical problem, with cancers and neurological diseases seen as diseases of aging." Cardiovascular research made major advances then, achieving such milestones as statins and stents.

"There was good progress in cardiac medical therapies. But now cancer and neurological diseases are the two major problems facing our society," he said. For the former, there is abundant progress and hope: "Cancer etiology is complicated, but we have new drugs, with the recent Tang Prize awarded for this work."

In contrast, he noted that "There are no good neurological drugs" to treat such major diseases as dementia, Parkinson's and Alzheimer's: "We don't even have a good drug for Parkinson's disease; levodopa delays but cannot stop its course."

Taiwan's Ministry of Education is soliciting proposals for research and education programs in a major push for progress, Chairman Chang said. The TMU team, led by President Lin, is putting forward proposals for neurological programs to compete in this critical area.

TMU's 'big three' priorities

The university's current research prioritizes three vital societal needs: Taiwan's high cancer death rates, its vast human toll from traumatic brain injury, and the looming demographic challenges of becoming a "super-aged" society.

"First, we are focusing on translational cancer research, including research on 'personalized medicine' approaches to therapy and drug development," he said. This research will especially try to address colon and breast cancers, which are among the top killers in Taiwan.

"Second, we are focusing on brain and neurological research. This brain research is very important for an aging society like Taiwan's," he said. This year, TMU started a Neurological Research Center based at Shuangho Hospital that involves more than 70 doctors—both attending physicians and researchers—in this research, plus another 30 support staff in areas like bioimaging. TMU also plans to build two high-rise buildings that will vastly expand the Shuangho campus's educational and research operations.

"We hope that since the center started this year, it will also give our students a better-integrated research perspective," Chairman Chang said. This effort builds on nine years of collaborations between surgeons and neurologists who attend a weekly meeting to discuss cases and findings. Together, these efforts address the traumatic brain injuries associated with scooter transportation as well as Alzheimer's, Parkinson's and other brain diseases.

The university's third priority research area is aging. A recent strategy meeting at Wanfang Medical Center discussed that hospital superintendent's research collaborations with Nagoya and Matsumoto.

This followed a TMU fact-finding delegation's visits to both cities that studied Japanese gerontological care approaches that might offer useful insights. As the Ministry of Health and Welfare is developing long-term care and other services for Taiwan's elders, TMU is supporting these efforts with both clinical and basic studies.

In terms of predicting future directions for progress, Chairman Chang said biomedical research is progressing the fastest. For example, the time required for human genome analysis has fallen from five years to just 30 minutes using new technologies. "You can see that the progress is fast, but we need to focus on 'What are the medical needs?'" he said. TMU is doing this with priority research programs in neurology, cancer and geriatrics that address the most pressing needs of today's health care systems.

How changes affect students

The university's educational and service missions are being transformed as well. For example, TMU started requiring a computer software "coding course" this year to help students add more to their clinical and research fields.

Other changes look far beyond the TMU campus to engage useful educational resources. "In the 1970s and 1980s, many Taiwan graduates went to the U.S. and U.K. for postgraduate studies – but now we have the problem that they want to stay in Taiwan," the chairman said. "This is not good: Taiwan needs to globalize."

The university's answer to this problem has been to increase programs that encourage outbound students to make use of opportunities abroad, and to promote these opportunities with funding support and expanded publicity.

Chairman Chang said another change from his own era as a student at Taipei Medical College is a vast expansion of English-friendly programs and international student recruitment: "I'm also glad to see so many international students presenting in English and asking questions at TMU events. It's a good educational environment now."

Yet he spoke of other changes over the decades, particularly the much greater pressure on students to compete with professional publications. "In our era, if you wanted to purify a protein, it took three years. Now it takes one week. Molecular biological tools make these tasks very easy, but the progress of research makes competition tougher. … Now high impact factors are important in building careers."

It's harder to recruit young researchers because they consider this pressure, and they wonder whether they will have enough ability to succeed, Chairman Chang said. "For example, I'm involved in the selection of winners of the Tang Prize [awarded biennially in Biopharmaceutical Science and other fields]. Last year (2016) it went to a very young researcher in MIT, only 35 years old." But his work on CRISPER/Cas9 contributions earned him this prestigious global award together with two other distinguished scientists.

"If you have a good idea and study hard, you can do a better job than we did. But even then, we had to work nights and weekends," he laughed. His advice to young researchers takes the faster pace of scientific progress into account, but does not candy-coat the difficulties they will face: "You have more opportunities due to these better tools and reagents. This helps balance the tougher competition—but there's no question that you must make more effort."

Why Taiwan chose TMU to lead stem cell research

Prof. Rita Yen-Hua Huang and her students speak

"TMU leads the nation in systemic cell therapies and regenerative medicine," Distinguished Professor Rita Yen-Hua Huang noted in a recent talk. As proof, the Center for Cell Therapy and Regeneration Medicine's director noted that TMU triumphed over 20 universities to host the National Program for Regeneration Technology Development.

But pre-eminence doesn't mean she's working alone—the young center already cooperates with five U.S. universities and one U.S. company, four Taiwan companies, a Korean university and hospital, two top Japanese universities, and both Hong Kong University and the Duke University-National University of Singapore Medical School.

Prof. Huang's presentation was occasioned by the visit of Stanford University-based stem cell pioneer Prof. Irving Weissman, who uses embryonic stem cells in some of his work. Because these cells come from fetal tissue donated through the U.S. Anatomical Gifts Act, certain religions also oppose this research, and government and universities are wary of supporting it. In contrast, Taiwan has been free of opposition to cell therapies because the TMU lab uses mesenchymal and small blood stem cells, not embryonic stem cells. Prof. Huang said Taiwan's government made a "top-down proposal" offering grants so Taiwan can develop this vital biotech area. TMU was ranked first of 21 applicants, and she anticipates renewal of the three-year Ministry of Science and Technology grant.

Although each six-month review has gone well, the best guarantee of this research continuing is a tangible, practical solution enabled by the lab's research: "They want a product," she said. A wound patch for the slow-healing skin sores that plague diabetics looks like one likely candidate, but the center is developing plenty of other ideas and moving them toward clinical trials.

These efforts have four supporting parts: university educational programs, TMU Hospital participation, animal labs for pre-clinical studies, and a Good Tissue Practice (GTP) cell culture laboratory that serves as the incubation center for clinical-grade cell preparation. GTP is an international standard for lab safety and quality, based on a 2005 U.S. law regulating use of human cells and tissues as well as products based on these. TMU pursues research into both stem cells and non-stem-cell immune therapies under these demanding conditions.

The lab's work so far spans from basic research through pre-clinical animal studies, with a triple focus on 1) stem cells and regenerative medicine, 2) use of these techniques in translational medicine, and 3) development of ethical outreach and educational services for industry and society. The translational focus combines the work of doctors, scientists and businesses to find safe and effective new techniques that address unmet medical needs.

GTP Core Laboratory

Beyond 'bench to bedside'

Prof. Huang expands the traditional "bench to bedside" model as "3B+E": bench, bedside, business, and education. For the "bench" or basic research, she says the center's main efforts are in studying niche and embryonic pluripotency (niche hypoxia and inflammation), stem cell immune modulation and epigenetics, and nanodrug and cancer stemness.

The "bedside" or clinical promise is pursued through preclinical studies in which mesenchymal stem cells and small blood stem cells as well as immune-related mechanisms (natural killer cells, T cells, CAR-T) are being used to treat cancer, decubitus ulcers (bedsores), severe burns and multiple sclerosis. The center's innovations that have moved closest to clinical trial stage involve guided bone regeneration in implant surgery using small blood cells, and a patch to heal diabetic foot ulcers that involves both small blood cells and mesenchymal cells.

Taiwan's Food and Drug Administration is reviewing a strategy that uses small blood cells in dental implants, which Prof. Huang says is very promising for Taiwan's aging society, noting that a large number of the elderly endure the discomforts of dentures.

The field is very young—only 55 cell therapy products have been approved on world markets, she

said, with Japan providing 4 and the US more than 20.

Different countries have different regulations, and to protect patient safety Taiwan is fairly conservative compared with the global spectrum, so the TMU team is awaiting permission to progress to phase 2 and 3 trials. Although they cannot patent the cell components, the delivery systems are patentable, so the team is perfecting the sheets and glue used in the wound-healing patches.

TMU's GTP lab allows businesses to rent space alongside scientists to develop products in a safe and government-approved environment. Prof. Rita said the lab has received good level of interest from the commercial sector. It also offers TMU's affiliated hospitals and doctors support in developing their research.

Of two immune-based cancer therapies under development, one uses natural killer cells, a non-stem cell, and is in Phase 1 trials. The current three-year grant will cover finishing this phase next year, with the next phase tentatively scheduled for 2019. If this goes well, it will be offered for industrial development to support the costs of Phase 3 testing. The principal investigator retains ownership of the patent on behalf of the research team, so industrial development does not mean that TMU says goodbye to the positive outcomes of this research, including profits.

GTP Core Laboratory

The educational mission

Prof. Huang said it is unusual for students to be involved in such research, but she has company in that assessment: Prof. Weissman called TMU's MD/MS program "unusual and exciting" because it combines clinical and research components, allowing medical students to study cell therapies and product quality control.

The center also recruits degree students for the International PhD Program for Cell Therapy and Regeneration Medicine worldwide: these students often have professional experience with industry or research in their home countries.

Another proposal will help the lab provide general education programs for patients and others if it is funded by the Ministry of Education. TMU undergraduates already can take elective courses to learn more about this new field, and the degree program has more than doubled its enrollment in its first two years. These students are investing in a research degree, and three students who accompanied Prof. Huang to a recent interview were clearly aware that this new field is different from traditional pharmaceutical research.

Scott Yi-Heng Lin has been in the cell therapies master's degree program since its initial year. He said pharmaceutical companies cannot commercialize these therapies as drugs—after all, they are "personalized medicine" tailored to each individual case, not administered as factory-manufactured standard doses. This means researchers must rely on other funding sources.

First-year student Ngo Thi Mai Huong agreed that it's hard to get research money from pharmaceutical companies for these topics, like her studies of pathways and resistance in liver cancer. Ms. Huong has a deep background in research, with a decade of lab experience in Ho Chi Minh City and Haiphong in her native Vietnam, most recently studying in-vitro fertilization.

Another first-year student, Ageng Brahmadhi, went further to say that not only is each case unlikely to yield profit, but for now at least, these techniques are still "cost-consuming." Thus he said that the issue isn't pharma acceptance yet, but instead proving safety and efficacy so that companies will be willing to develop cell therapies on a larger scale. "First we must translate safety; safety is the biggest consideration," he said. "Getting industry money is still far in the future, after many more stages. For now, the research relies on government funding."

Mr. Brahamadhi was recruited from Universitas Muhammadiyah Purnokerto in central Java, with a background in medicine as well as histology and cell biology. He is working on DNA methylation, looking for biomarkers that will be useful in cell therapy.

Indonesia is another context for stem cell controversies, with cell therapies being pursued seriously by only two big hospitals in Jakarta and Surabaya. However, he said that private clinics promote scams that are marketed as stem cell therapies, based on myths that need to be countered by education for both patients and clinicians. Part of the problem is that few Indonesian-language publications cover this new field, and because most doctors do not study English in medical schools, they are cut off from international scholarly journals.

Dr. Lin has been working on finding mechanisms of acquired resistance in cancer biology, hoping to understand how this works and is overcome. He said that the dual-degree program could be pursued at various points during medical studies, with students generally starting their research in their fifth year and completing the degree in the sixth. But he advised students to start earlier, perhaps even in their first and second years, saying the earlier these students can get into research, the more time they can spend on this, because the medical school curriculum becomes more demanding as the years pass: "There are so many other things to do."

He knows this first-hand, because he entered the program after receiving his MD degree. After seeing heartbreaking critical care cases where "there's really nothing more we can do for the patient," the promise of using cell therapies to address these medical challenges makes the program rewarding.

He says that addressing problems like a scientist rather than a clinician helps him to "think logically and critically" rather than applying received protocols and care standards, as physicians do. "The program is more structured and evidence-based [than medical school], and we learn skills and techniques" that doctors don't encounter. For these reasons, Dr. Lin praised the TMU MD-MS option as "a really good combination."

Prof. Huang (right) with her students (from right to left), Scott Yi-Heng Lin, Ngo Thi Mai Huong and Ageng Brahmadhi

TMU Spotlight

Four surprising insights from a life in the lab Stanford stem cell research pioneer shares advice with students

The circular conference hall was packed for Stanford University's Prof. Irving Weissman's talk on Normal and Neoplastic Stem Cells: Biology and Clinical Translation. But there should have been laughter when he opened by saying, "Stem cell biology is very simple."

The crowd didn't know that this eminent researcher would take off at a run, recapping dozens of complex findings since 1988, when his team published on the first isolation of a body stem cell—the blood formingstem cell in mice, and then a few years later the human blood forming stem cell as tested in irradiated and immune-deficient mice that had been grafted with human fetal blood forming tissues.

An early slide playfully said In vivo veritas [In life is truth] - a pun on the Latin in vino veritas, or "in wine is truth." Prof. Weissman has spent nearly 60 years chasing truth in labs, leading to results in the 1960s that enabled human organ transplants.

Yet there might have been seriousness in the pun as well. Because live stem cells are infinitely more useful than dead cells often stored for research, he urged researchers and funders to maintain live cell lines for future experiments.

Growing up in Montana, he learned research skills early in a pathologist's laboratory, then chose Stanford medical school because its program allowed half-day clinical training that let him continue his research the other half of the day. This experience that led him to praise as "promising and unusual" TMU's MD-MS and MD-PhD programs that offer the same dual expertise.

But he wouldn't continue with two careers; he said no to the internship training that would have followed the MD degree so he could focus on research. (His advisors said he'd regret this. He doesn't.) So he's been chasing big questions in Stanford's labs since the 1960s, eventually helping to test the Herzenberg cell sorter that made stem cell research possible when "we got pure blood-forming stem cells."

These results showed huge potential, and he formed a company called SyStemix to sponsor testing that showed effective depletion of cancer and T cells from patient blood forming tissues. That led to a clinical trial in which women with widespread [metastatic] breast cancer were rescued from high dose potentially lethal chemotherapy with their own cancer-free purified blood forming stem cells rather than the conventional method that didn't purify the blood forming stem cells from cancer-contaminated mobilized blood. That study in breast cancer patients led to incredible results: half of the patients rescued with unpurified mobilized blood died within two years, but those receiving cancer-free stem cells half died in ten years - results still unmatched by conventional therapies. Fifteen years later only 7% of the patients receiving mobilized blood were alive, but now, 20 years later, 33% of those patients rescued with purified stem cells are alive without cancer.

Name: Irving Weissman, MD
Education: BS, 1961, Montana State University; MD, 1965, Stanford University
Present appointment: Director, Stanford Institute for Stem Cell Biology and Regenerative Medicine; Director, Stanford Ludwig Center for Cancer Stem Cell Research; Prof. Pathology, Developmental Biology, Biological Sciences, Neurosurgery

Don't read the paper!

Although the talk kept the crowd rapt well into overtime with its vast scope and erudition, Prof. Weissman's greatest contribution may have been his unexpected advice to TMU's MD-PhD students.

His surprising first suggestion was: *Don't* read promising scientific papers … at least not at first. Instead, look for papers with interesting titles – and stop at the title. Consider it a challenge to figure out what the authors were studyin, then design an experiment that would test what the title promises.

How would you do it? What kind of proof would be needed? What materials, what costs, what numbers? Once you've sketched out your own ideas for an experiment, only then should you go ahead and read to see what the authors did. Then compare the two approaches and learn from this to make better guesses next time – and to design your own experiments.

"To get to this point, you need some background" from classroom training, he said. "But you're passive [in classes] – be active!" If you stop at the title, you have the real problem in front of you to solve. And at least one good, peer-reviewed answer is there to teach you when you read the rest of the paper.

This habit of independent inquiry is essential to scientific thinking. Universities must teach received wisdom because they cannot teach what hasn't been discovered yet, and aren't very good at asking students to think beyond what is known.

"You learn one thing and you're overconfident: I fault medical education for that," Prof. Weissman said. "Luckily, textbooks are found wrong quite often – but if their pearls of wisdom are unquestioned, students are not equipped to understand alternative approaches."

Go where the action isn't

Prof. Weissman's next piece of advice also questioned conventional definitions of scientific success. He advised students to think less about chasing a new drug and think more about the problem they want to solve – and don't be seduced by seeking a commercially viable solution.

"The money in the past century has been in small-molecule drugs, but they're not where all of the action is," he said. "In fact, they have greater potential to cause harm at other body locations and organ systems, even if they prove useful in other limited contexts."

The economics of big pharma dictate that "it always has to start again" to get a winning product it can protect with a patent. "But small molecules are often toxic to normal cells, and because in cancers the targets of small molecules are proteins, and in a mutant cancer cells the amino acids can change, and the cancer cell with that change can be resistant to the drug. In fact, mutations are a sure thing, and in a cancer of over a 100 billion cells, a naturally resistant cell likely already exists."

Because cell therapies present patenting issues that make big pharmaceutical companies hesitant to invest in them, he said, "No small molecule pharmaceutical company was in on the initial discovery of protein therapeutics, and no protein therapeutic company discovered a cell therapy. Each develops its own culture and how to make a business from its speciality. "

Stem cell therapies are different because stem cells from healthy donors have the full collection of normal genes, so that they can regenerate a system that has multiple genetic errors. Immune cell therapies target whole proteins, and even some amino acid changes don't remove the multiple targets on those proteins. That's why they can address slow-growing mutations like those associated with cancers

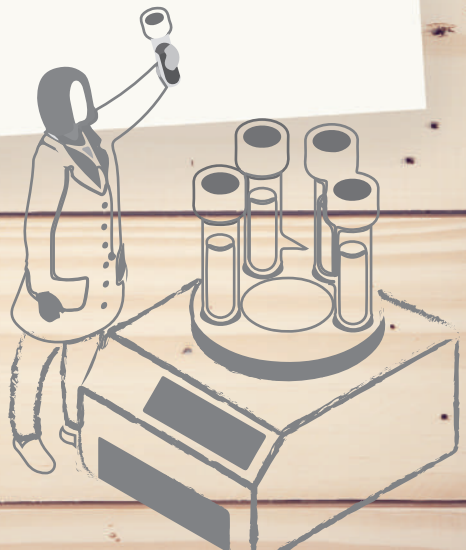
Then Prof. Weissman had a question for his audience: he asked the students how they would choose their post-doc lab. One student said he'd look for one that does research similar to his expertise.

Wrong, Prof. Weissman said.

"Your postdoc is your last, best chance to start your career. So choose a program that produces many successful researchers – not a lab that has a Nobel-winning star or that specializes in your interest area. Otherwise, he said, it's hard to judge what the lab can give you.

You're not looking for bragging rights from a big name; you're looking to get the good habits that have produced other successful researchers. Better to train in a "boring lab"!

TMU's eminent Prof. Jacqueline Whang-Peng disagreed with this. The "mother of cancer research" in Taiwan said students should choose a program that both provides basics and gives some glamorous distinction – "because you need something impressive" to provoke interest in you during that next competitive job search. Prof. Whang-Peng is director of TMU's Taipei Cancer Center, now under construction, and was the first female scientist at the U.S. National Institutes of Health in the 1960s.



Don't sweat the job search

Prof. Weissman took a sunnier view, telling students that bioscience doctorates would surely get them a satisfying job in the field, because there are lots of good bioscience careers beyond lab and faculty positions.

He asked the students to guess the percentage of bioscience PhDs who cannot find jobs in their field of study. They didn't volunteer any estimates, so he noted that a survey asked the same question. Given the great pessimism prevailing in higher education, he said, responses usually were upwards of 30%. The reality? The researchers found that only 1.5% of life science PhDs were not working in a field relevant to their training.

"So don't think about going on to business school" if you're not setting the world on fire with your research, Prof. Weissman said. "You're not a failure" if you go to work in a patent office, for example, because "patent offices keep you close to research" – and you can play a very useful role supporting science there or in other government agencies, or other positions that require a knowledge of bioscience.

He told students that if they found their studies rewarding, they shouldn't let fears of joblessness drive them away from science – there's a career waiting, even if it's not running one's own lab or competing on the tenure track as a professor.

A corollary to this was his last piece of advice to the TMU students: If you're not excited by lab life now, don't plan on spending the rest of your life there. Many other opportunities exist, and they may not put as much strain on family life as the often 24-hour demands of scientific experiments.

But well into his 70s and still deeply involved in research, Prof. Weissman has no complaints: "It's a good life. That's the price you pay for all this fun."

The money or the lives?

Prof. Weissman's secret for research success was to "Think about how your discovery will help people – and this means that you refrain from commercializing it right away." Don't take the money and run toward another research direction, he said, because no one else can do as good a job of developing the potential of an idea as its discoverer, who's already spent years on that idea.

"The person best suited is the person who made the discovery; they should carry it on toward practical applications," he said. "I know people who had an idea in 1960 who are still working on it," mining those topics with downstream questions and developments.

"All applications make money for somebody. But academics stop and hand theirs to businesses too soon, in part because of the huge costs involved: from one to three billion dollars" is invested in each successful drug, Prof. Weissman said.

"That's why drug companies are amortizing failures on the backs of their successes" by making business decisions to protect their winners at all costs, he said. This includes blocking promising new approaches, such as the breast cancer cell therapy trial that was shut down and effectively buried by its big-pharma buyer for 12 years.

So while businesses must put profits first, scientists can remain faithful to their ideas. "So far everything I've discovered has worked – because we stayed with it," he said. "When we tried a novel antibody therapy in non-human primates, it burst their red blood cells. But we kept at it, made another antibody to the same cancer target, and now it is in late phase clinical trial for humans."

His own career echoes this, he said: from an idea in 1975, "it took a long time" to bring this to fruition. He created the SyStemix company "because no one else wanted" this idea. But after losing the promising breast cancer idea, and many other blood stem cell applications to a big pharma company, he didn't stop fighting.

"It's taken 12 years to get back the cells antibody forming cells that made antibodies to isolate pure blood forming cells; I gave away stock and helped raise 200 million dollars for our Institute of Stem Cell Biology and Regenerative Medicine at Stanford, and our med school/hospitals/university have established a novel facility to purify blood forming stem cells for all of the applications we wished to test" Prof. Weissman said. But meanwhile, he said, fifteen thousand women with metastatic breast cancer keep dying each year that could be saved by this cell therapy. "That's why you want to keep business out of research until your findings will clearly make money for their shareholders. Then you can hand it over and it will move forward."

Penn State partnership evolves from friendship to multiple programs

Dual degrees, neuroscience cooperation and summer exchanges blossom

Interview with Dr. Wenke Huang (right) and Ms. Carol LaRegina (left)

TMU has partnered with America's famous Penn State University in several areas, including signing agreements for neuroscience collaboration and nearly finalizing plans for an exciting joint degree program.

The architects of this cooperation from Penn's College of Medicine and its Public Health master's degree program recently visited TMU to share two lectures and to finalize the dual degree program and discuss the two-way summer exchange programs for medical, pharmacy and public health students.

The exchanges are now enrolling their third annual cycle of participants, but the partnership might be traced back more than eight times that long, to Dr. Wenke Hwang's friendship at Johns Hopkins University with Dr. Nai-Wen Kuo, a TMU public health scholar who would later become dean of College of Public Health.

Twenty-five years later, this personal link has borne fruit not only with students going both directions, but also common research interests. Dr. Hwang lectured in November on "Quality of Care Measurement as a System Improvement Tool" and joined a health policy class to talk about "Multi-site Health Records Research and Subject Protection."

The partnership has grown since a casual dinner in 2012, supported by institutional travel grants and student scholarships. "TMU has quite a few attractions," Dr. Hwang said. "It has vibrant leadership and has

followed up with a lot of interest. A lot of partnerships don't result in much, but this one sort of clicked." He credits former President Yun Yen with showing that the partnership was a high institutional priority, "so I knew this was the right direction."

Because Penn State's MPH (Master of Public Health) program is an important supporter of the exchanges, the program's Associate Director Carol LaRegina made her first trip to Taiwan in November to discuss the joint dual degree program, which with only one year of study abroad is expected to offer both US and Taiwan diplomas. She said she found Taiwan's academic climate "very interesting, and your [TMU] students are excellent. We're very excited about this partnership."

Dr. Hwang concurred: "'Enthusiasm' is the right word to describe this collaboration." He had briefed last summer's six Penn State students as they prepared for their research in Taiwan, and said "Before they come here, we tell them to study TMU, so we can make use of experts here that share an interest in their topics. That way they can take advantage of this opportunity."

TMU has sent two to three students per summer so far to the Global Health Exchange Program (GHEP) at Penn, where they participate in an intense schedule including meetings with state lawmakers and health officials, a community volunteer opportunity, and presentations where they exchange with Penn State public health students. The students usually take a weekend to see New York, and they visit Washington D.C., to meet with national legislators on a field trip from the Hershey campus.

Ms. LaRegina said that a Penn State student service group offers hospitality with a picnic, party or barbecue, and that other students come from around the world to join the group; last year's team included students from the Netherlands, Georgia and China. Penn State students can participate in GHEP as well and receive three credits.

As for the inbound students who come to TMU, Ms. LaRegina said that their master's students must focus to finish in two years, so there's less time especially for second-year students to write up their Taiwan research for publication, although they do participate in a shared blog and by journaling. One student's essay about her Taiwan experience landed her the very competitive paid position of two years as a legislative research fellow—a nice graduation present indeed.

Meanwhile, two medical students are finishing another professional journal article based on their TMU research with Taiwan co-authors, with one paper already published the month after they left Taipei. Ms. LaRegina notes that this was only possible because the TMU faculty member supported these students in learning SAS so they could perform the statistical analysis, an ambitious summer project on top of the research itself.

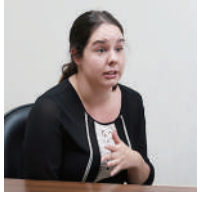
The joint degree program is moving forward, with enrollment expected to begin in 2019 at TMU and 2020 at Penn State. Biomedical majors and nutrition students can extend their medical, pharmaceutical and public health studies one year and receive the two credentials—which the Penn State team noted presents a cost savings of about half over pursuing the two degrees separately, as well as the greater career mobility of graduate degrees from two nations.

Dr. Hwang described the partnership as "very incremental, step-by-step—a deliberate progress" from the Memorandum of Understanding to the joint degree talks and summer exchanges. In 2013 and 2014, a neuroscience team signed an agreement for cooperation in that area, and in fact a Penn State neurosurgeon recently spent a month working with the famous brain injury registry associated with TMU's former President Wen-Ta Chiu, who was Taiwan's Minister of Health from 2011 to 2015.

Before the faculty visit, the six summer students who came to Taiwan shared their thoughts in earlier interviews; all said they would recommend the TMU experience to their fellow students. With the exchanges enrolling for next summer and the joint degree program expected to open for applications next fall, TMU's Penn State connection has blossomed from a friendship to change many lives for the better.

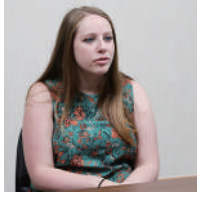
Exchange students go both ways to compare health systems

Before the Penn State faculty visited to discuss expanding cooperation with a dual degree program, the six students who came to Taiwan shared their thoughts, as did one of three TMU students who went to the U.S. All said they would recommend the Penn-TMU exchange program to their fellow students.



Alexis Reid had an ambitious proposal for her summer research at TMU: "I would like to do a cross-examination of both countries and see what is being done well, cost-effectiveness, and things of that nature. I will learn about how the Taiwanese deal with environmental health regarding their country and how it differs from the United States."

Ms Reid had interviews with national health insurance specialist, home health care practitioner, and the director of Family Medicine about "rising cost of end-of-life care and how that could be." After her summer research, Ms. Reid reflected on what the TMU experience had given her: "My concentration is in health policy research on older adults and end of life care, and how it differs from the United States.



Jillian Miller also studies health policy, and continued to pursue her interest in electronic medical records at TMU: "I think your team went above and beyond in terms of helping us, and I think my only advice for the students would be 'don't be afraid to reach out.' My personal [block] before coming here was that I didn't want to just cold-call or ask someone here without any sort of connections—but I think that would have been completely fine. So I think that's something that would have taken advantage of it if I could go back."

Raymond Kim: "I'm a medical student, and I came with the intention of hoping to do some service clinical research… I started reaching out to as many physicians in the fields that I was interested in…I got in touch with one of the orthopedic surgeons … he was very enthusiastic and he actually set up a meeting immediately with one of the public health professors who was an expert with using the national health insurance database… our plan is to communicate via Skype and email once I get to the US. We hope to do some sort of a cost analysis between total hip replacements in Taiwan versus the United States.

Anna Marie Warrington's proposal focused on comparing health outcomes and costs in the two nations: "The United States could definitely use some guidance when it comes to health care reform and I think it is pertinent that health care policy makers take notes from other countries, like Taiwan, who have successfully implemented and gone through health care reform."

Reflecting on her study during the program, which looks at the cost of elderly dementia care and quality of likfe in Taiwan versus in the US: "We were a little shocked to see the similarities between the US and Taiwan even though they're very, very different structurally." Ms Warrington noted that both Taiwan and the U.S. are having a very rapid increase of the elderly and are "having a really hard time paying for elderly care, especially dementia care… Taiwan's elder care system is largely non-institutionalized, but if you have a very physically dependent dementia patient it's more cost-effective to have them in institutionalized care than in-home private care, and that's the same in the U.S. as well."

Nd Ekpa proposed "to study end stage renal disease (ESRD) in the context of universal health care to determine the genetic, cultural, and/or behavioral components that make ESRD so prevalent in Taiwan. I also hope to explore the cultural influence [on ESRD] through first-hand exposure and cultural immersion. Finally I want to compare these findings to what we see here in the United States to see the strength and weaknesses of both systems."

"The big reason I came was this card system, the health care system, because I hope to do something along the same lines in my future practice. [For medical students], ours is a longitudinal partnership—so we come here between the first and second year, and are supposed to come back again during the third and fourth year."

Emily Kostek's proposal: "We've heard that Taiwan's health care system is highly successful…My goal for this program is to take something that Taiwan is very good at and compare that to the United States. … I am interested in health outcomes, such as chronic diseases and how they are affected by and dealt with under Taiwan's health care system."

"I'm working with Jillian on EMR (electronic medical records); she's focusing on policy, as she's very interested in the electronic medical records and biology. I am interested in disease control, and so we are looking into electronic medical records and how they can control diseases.

"And so we were looking at the SARS outbreak that happened in 2003, and we're going to the CDC (Centers for Disease Control) today so I'm hoping that we'll get a summary of their experts' personal experiences with disease control and the SARS outbreak in 2003. Basically we're learning a lot about the EMRs."

Chia-Liang Liu went to Penn State's international public health summer program with partial support from a TMU grant. He praised the Penn program as "compact" in terms of a great reward for a short time commitment. Mr. Liu's interest is risk assessment relating to lead poisoning, and his research focuses on absorption and uptake in animals that drink tainted water. He is part of the TMU public health team that has cooperated for nearly a decade with the U.S. Environmental Protection Agency.

Mr. Liu advised other students to make use of this opportunity: "Study the schedule, and know what you want to learn. And be ready to speak English! We went to Philadelphia on the weekend, and people were really friendly." He said he expected more lab time and internship work, but that the structured experiences were more interesting. In summary, he called the program helpful, and said he looks forward to getting a U.S. master's degree.

'Silent epidemic' of delayed brain changes holds huge implications for mTBI patients

Renowned US neuroscientist Prof. Barry Hoffer calls his decade of ties to TMU "fortuitous." The link between his National Institute on Drug Abuse (NIDA) Scientific Director position and TMU began when Prof. Yung-Hsiao Chiang joined the faculty in 2007 to conduct stroke research. Prof. Hoffer laughed that his post on a premier agency for funding neuroscience made him "a big vacuum cleaner collecting promising students" for research into addiction, Parkinson's disease, stroke and brain injury.

Prof. Hoffer has since retired from the National Institutes of Health, but he laughs as he says that's a misnomer: "No one ever retires from NIH – you work just as hard, you just don't get paid for it!" He has taken on a professorship at Case Western Reserve University, and calls the three-way collaboration between the US science agency, the eminent U.S. research center and TMU "very productive." In fact, the ongoing joint research project has been funded continuously for more cycles than almost any other existing joint project.

Prof. Hoffer says he's "happy to return to science" after 15 years in the NIDA scientific directorship, and that he likes being "back in the trenches." He praised TMU as offering great expertise in basic and translational medicine, but more than that, he said its faculty and students are exceptionally smart, hard-working and innovative. "I often tell my US students I wish they worked as hard" as Taiwan researchers do, he said with his characteristic good-humored chuckle.

It was Prof. Chiang's research into stroke and traumatic brain injury (TBI) that involved Prof. Hoffer's frequent visits to TMU, as well as two scheduled symposia on this topic to share research results each year. Other TMU researchers, labs and projects are pursuing answers to these questions through basic research, animal models and translational medicine – the full range from "bench to bedside."

Prof. Chiang's team is part of TMU's neurotrauma research complex, which was ranked third worldwide under the presidency of Prof. Wen-Ta Chiu. That neurosurgeon spent years promoting Taiwan's mandatory motorcycle helmet legislation after seeing a fellow student's promising career destroyed in an instant by a scooter accident. He continued to pursue his quest to prevent and relieve suffering from brain injuries during his years as superintendent of two TMU hospitals as well as his presidency and later role as the nation's Minister of Health. His legacy is the university's dedicated center for this research (the Neural Regenerative Medicine Ph.D program) as well as opportunities for advanced research with international partners like Case Western Reserve University.

TMU's new president, Prof. Chien-Huang Lin, is building on this legacy in a major way and envisioning a Neuroscience Medical Center that will share the same prominence and level of support as the TMU Taipei Cancer Center. Clearly TBI is a major public health problem, whether from Taiwan's scooter-oriented transportation or wartime blast injuries: both types of trauma send many thousands of survivors into disability.

And this is where the silent epidemic becomes truly terrifying. Eighty percent of brain trauma is classified as "mild"—as Prof. Hoffer says, the ER doctors

Interview with Prof. Barry Hoffer (right) and Prof. Yung Hsiao Chiang (left)

shake your hand and tell you you're lucky to have no visible brain injury.

Prof. Chiang and Prof. Hoffer's recent findings contradict this, noting what the latter called "an interesting progression" of depression and anxiety (often classed as PTSD, or post-traumatic stress disorder), Parkinson's disease and early-onset dementia. The helmets keep the brain anatomy intact, but Prof. Hoffer says that they cannot protect survivors of mTBI from these sequellae that often render them unable to keep their jobs within months or years.

A study that began in 2009 has been tracking 575 brain injury patients who were found to have "spontaneous recovery" within six weeks—but within the next year, many complained of dizziness, depression and anxiety.

Prof. Hoffer calls this toll from mTBI a "domino effect"—a cascade of symptoms that are unexpected, and so are usually left untreated or treated inappropriately: "They're sent to a psychiatrist who sees nothing wrong, and who sends them away with a prescription for an antidepressant."

The key is finding the evidence—because the usual neurodiagnostic tools, CAT scans and MRI images, are useless in locating the biochemical changes and consequent changes in gene expression that trigger this disaster. Without diagnostic criteria, these eighty percent of all TBI patients cannot get help when they lose their jobs and their ability to function at their former levels.

The team's recent papers in Cell Transplantation and the Journal of Biomedical Science show promise in this area—but also a tragic clue to the high levels of addiction found among TBI patients.

Apparently dopamine expression is affected by brain trauma, so US veterans who suffer blast injuries have a tendency to "self-medicate" in an attempt to restore normal dopamine levels, Prof. Hoffer said. Dopamine controls emotions and affects memory, so this finding explains why even "mild" brain impacts—not involving loss of consciousness, and often described as "anything that makes you see stars"—can have such profound effects.

So now research teams like the "brain project" supported by Taiwan's Ministry of Science and Technology can start the observational clock at the time of impact—not when the distressing symptoms start months and years later. They are also closely evaluating animal studies for biomarkers as well as behavioral and electrophysiological results.

Prof. Hoffer modestly says he's a "team-builder," and that this is easy because these researchers are often people hired for their excellent work. Some work with stroke, aging and dementia, all increasing problems in Taiwan's fast-aging society.

But he said Taiwan leads in mTBI research, and that until this research, PTSD wasn't even strongly linked to brain injuries. So with 70% of Taiwan's vehicles still being scooters and motorcycles, both USA and Taiwan have a huge stake in solving the puzzles of this silent epidemic.

"We didn't expect these results," Prof. Hoffer said. It was the data from each U.S. hospitals that showed the pattern of blast victims encountering serious difficulties much later. They are just seven years into this cohort study—yet high school and college

football players are turning out to have major functional debilities in their thirties and forties, twenty to thirty years after brain impacts that are not yet recognized as dangerous.

Asked about the magnitude of the problem, he was uncharacteristically somber. These implications are so big, he said, that "We have to watch what we say, because schools don't want to be held responsible" for young players' later disabilities. But as the evidence of "mild" brain trauma's huge toll in disability-adjusted life years continues to grow, this group of premature dementia patients will join the blast victims and vehicle accident trauma patients as a public health epidemic that is anything but silent.

The Center for Neurotrauma and Neuroregeneration Research

The unit has received approval from the Ministry of Education to establish the Neural Regenerative Medicine Program. In collaboration with the National Health Research Institute, the unit established the Center for Neurotrauma and Neuroregeneration Research. The center initially conducted nerve catheter clinical experiment in peripheral nerve trauma cases, and imported the results of the nerve trauma research to technology transfer and industry-university collaborations. In 2009, the center also worked with NIH of U.S.A., Sweden, and Israel in international research projects on mild brain trauma translational medical research. In 2010 the center again received funding from the Ministry of Health for the Center of Excellence for Clinical Trial and Research in Neurology and Neurosurgery project, to carry out the one-university-nine-faculty Taiwan neurological clinical experiment network integration operation. Due to the U.S. involvement in Afghanistan and the Iraq Wars, more importance has been placed on brain trauma in international research. Our research team has, over the course of 7 years, collected data on over 500 patients who suffered post-concussion syndrome due mild brain trauma, and tracked the blood and clinical symptoms and changes in these patients after the trauma over time, where the longest period is currently at 5 years. Although there is no visible damage seen in these patients, mild brain trauma may lead to neuronal inflammation, apoptosis, or decline in neuron function. There are individuals suffering from mild concussion seeking consultation at Neurosurgery clinics daily, where the cause of such injuries in younger patients are mostly due to car accidents, while in the older patients, it is due to falling or bumping into hard objects.

The center's aim and direction for the future are: 1) develop tools for the diagnosis and evaluation of mild brain traumatic injuries (mTBIs), 2) establish strategies for the treatment of mTBIs, 3) establish neural imaging diagnosis for mTBIs (e.g. N-back Working Memory fMRI), 4) establish biosignatures for mTBIs (e.g. Bmx), 5) evaluate the financial costs for mTBI biomarker treatments and standard treatments, and provide the most up-to-date cost-effectiveness, 6) the research and development of novel drugs for mTBI treatment, 7) New strategies for the treatment of Parkinson's Disease, 8) Search for novel genes that are involved in the differentiation of nerve cells during neurodevelopment, and explore the functional role of the neural lipoprotein Znf179 in polyglutamic expansion diseases and its possible therapeutic effects, and 9) establishment of a mTBI digital cloud network database.

In terms of research and development on brain traumas, the research group is focused on using innovative methods to assist in the initial diagnosis and treatment of mTBIs: 1) mTBI biomarkers, 2) functional MRI, 3) wireless intercranial pressure monitor, 4) precision treatment biochip for mTBIs, 5) prediction of possible occurrence of neurodegenerative disease post-mTBI, 6) early intervention and treatment of neurodegenerative diseases. The purpose of these research and development are: to estimate the degree of mTBIs; alleviate symptoms; reduce risk in surgery; to diagnose and predict possible neural diseases in the future during the initial stages of the injury; reduce the damage caused by brain trauma and the rate of neurodegenerative disease at a later stage, such as Parkinson's or Alzheimer's Disease, which will reduce the costs incurred on society.

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TMU-UCL research tracks eye movements to seek an objective measure of mental illness

TMU's Brain and Consciousness Research Center and Graduate Institute for Health and Biotechnology Law have joined forces with one of the university's most renowned European partners: Belgium's 600-year-old Université Catholique de Louvain.

Louvain Prof. Marcus Missal visited Dr. Tzu-Yu Hsu in November to set up a joint experiment with important implications for a better understanding of mental illnesses. Their findings could dramatically change both treatments and health policies.

The three-year project is testing whether eye movements are associated with severe depression and ADHD (attention deficit hyperactivity disorder), following Prof. Missal's successful use of this non-invasive method with Parkinson's patients.

"I'm interested in impulsivity," he said. "It's normal [for everyone], but with mental illness it could be increased. Moreover, some medical treatments could also increase impulsivity. For instance, in depression, it seems that serotoninergic transmission correlates with impulsivity." But why come around the world to conduct a study with TMU?

Prof. Missal praised the university's commitment and proactive approach to research. "Thanks to open-mindedness here, there are many patients" who can participate in this research, he said. The initial cohort is 30 patients and 30 control subjects without mental illness.

Watching for wandering eyes

The goal is a precise measure of impulsivity using eye movements as a tool. Patients look at a screen where spots of lights jump to different positions and have the—instruction to follow them with the eyes, performing "visually-guided saccades" [fast eye movements]. "Premature saccades" are twitchy or bouncing glances before the jump of the spot of light and these may be associated with pathology or responses to treatment, as was found in Prof. Missal's work with Parkinson's patients.

He said that this method seems reliable and

could be used in conjunction with other measures of mental problems, such as questionnaires and diagnostic observations.

Along with its low cost, freedom from subjective bias is the new method's potential value. Clinicians, scientists and health policy-makers have long sought such an objective measure for mental problems and responses to treatment.

People will come to the lab in TMU's Shuangho Hospital so the system can record their eye movements. These recordings will be analyzed alongside four other kinds of data on the same 60 subjects: EEG (electroencephalogram) images of electro-cerebral activity and magnetic resonance images of neurotransmitter activity in different parts of the brain, as well as with questionnaires and medical records.

If the eye movements show solid associations, this interpretive method may be eagerly adopted by the medical community as preferable to more expensive, invasive and subjective measures.

Progress with Parkinson's disease

Prof. Missal came to TMU for just five days on this trip, bringing his custom software and consulting with Dr. Hsu, then departing the day before testing was to begin. "It's all up and running so I can go home," he said. During his visit, he lectured on "Neurological evidence of a dual origin of temporal preparation" that provides useful insights into Parkinson's disease.

He's confident because "I did with Parkinson's patients another test of the same method. It is useful, though not (yet) as a diagnostic so much as a way of following the efficacy of therapy."

Dr. Hsu said there're some limitations about current psychiatric diagnostic methods because the nature of these methods is largely subjective reports based. As the progress in neuroscience research evolved, instead of relied on clinicians' experiences and patients' reports, scientific approach may provide objective evidence by analyzing and integrating the five types of behavioral, biological and neuroimaging information, the researchers hope that this method can contribute to psychiatric diagnosis although it is still a long way to go. The preliminary testing expected to be done by year's end.

Prof. Missal praised TMU's willingness to devote resources to this research, as "not many people can do that" (administer the four kinds of tests and provide medical records on a useful number of patients within two months).

He said TMU is outstanding because all needed resources and facilities work together: "Everything is here, especially people who want to collaborate. They welcome outside research partnerships."

A world of research collaborations

This TMU-UCL partnership is still growing, according to Prof. Missal: "I believe there's a desire to develop more collaborative projects. But we have to go step by step, and get to know each other before writing grants" to do more research. He said he would also be looking for ways to give Louvain students a chance to participate in TMU research and other exchanges.

This inter-university cooperation is in its 8th year since an initial visit by two Louvain professors in 2010. More recently, a delegation of 15 Louvain scholars came for a research symposium organized by TMU.

This conference resulted in the two sides finding "common interests at the experimental level—and papers are pending" from these projects, Prof. Missal said.

Dr. Hsu noted that her college (of Humanities and Social Sciences) is growing fast. In the past year, it has expanded from a suite on the main campus to also extend to offices in the high-rise Da-An Campus, as well as establishing research facilities at Shuangho Hospital. "Especially thank TMU and Shuangho Hospital for supporting neuroscience research," Dr. Hsu said. "It is never easy to build a cross-disciplinary neuroscience research team without people's support from TMU and three hospitals."

Research complements TMU teaching

She said faculty members are recruiting international students with neurological, neuroscience and humanities interests because "they're both based on humans, and everything is linked." The master's degree program is established and a Ph.D. program is eagerly expected to be approved soon.

Within its medical humanities mission, Dr. Hsu says her unit also serves the larger university by offering courses introducing students in clinical training programs like medicine and oral medicine to psychology. These basic courses are enhanced by the

teachers' expertise in biology and neuroscience research, which has resulted in many publications about neuroimaging and consciousness.

The Ministry of Science and Technology is supporting Dr. Hsu and Prof. Missal's research. Yet its greatest impact might be in the Ministry of Health and Welfare and in other health insurance systems worldwide.

If the eye-movement method proves useful, insurers everywhere can confidently expand coverage for psychiatric services that are currently under-covered due to difficulties in proving need with subjective criteria—once there is finally a measure of psychological dysfunction that is lower in cost and more objective and versatile than ever before.

Dr. Tzu-yu Hsu came to TMU after years at National Taiwan University and Oxford University. Her research interests in experimental psychology and cognitive neuroscience include the neural mechanisms of visual attention and visual short-term memory, and the role of the prefrontal lobe and executive function in conflict/inhibitory control. Her research has recently appeared in Current Directions in Psychological Science, Journal of Neuroscience, Behavioural Brain Research, NeuroImage, Human Brain Mapping, and Frontiers in Human Neuroscience.

Prof. Marcus Missal has a 23-year track record of neuro-ocular research, and is also an honorary senior research associate at the Fonds National de la Recherche Scientifique (FNRS), Belgium's top research institute. He has taught and conducted research in Paris, San Francisco and the University of Cambridge. He reviews for the Journal of Neurophysiology, Journal of Neuroscience, Experimental Brain Research, Cerebral Cortex, Journal of Vision, PlosOne, and Current Biology.

TMU's Graduate Institute of Mind, Brain, and Consciousness unites scientists, clinicians and philosophers who investigate the levels and contents of consciousness. We conduct research into normal and altered states of consciousness through a range of techniques, including multi-modal brain imaging and brain stimulation. The aim of our research is to advance the understanding of what consciousness is and how it can be impaired. We hope these advances can be used to develop improved diagnoses and treatments for psychiatric and neurological disorders. We offer a master's degree in cognitive neuroscience (PhD under way).

The Research Center of Brain and Consciousness investigates the levels and contents of consciousness, along with the cognitive mechanisms that modulate these. Central to this work is the use of different brain imaging and stimulation techniques to directly measure and manipulate brain actions and understand how these work in health and disease.

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