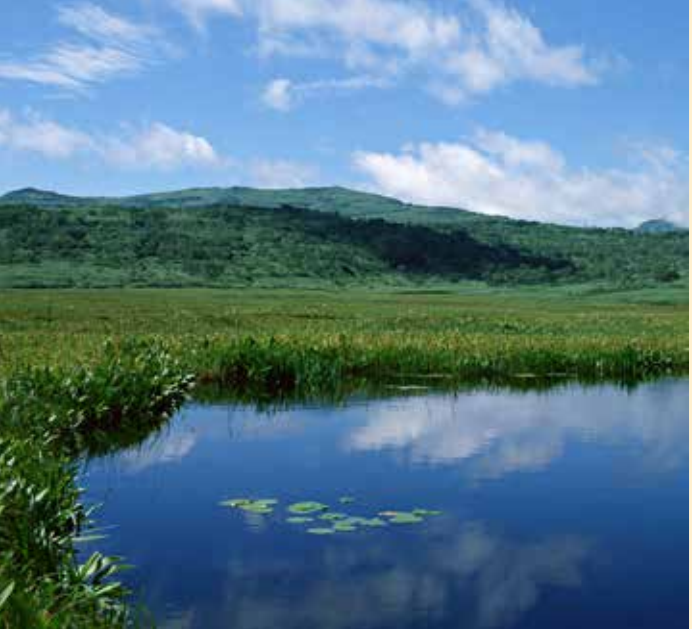


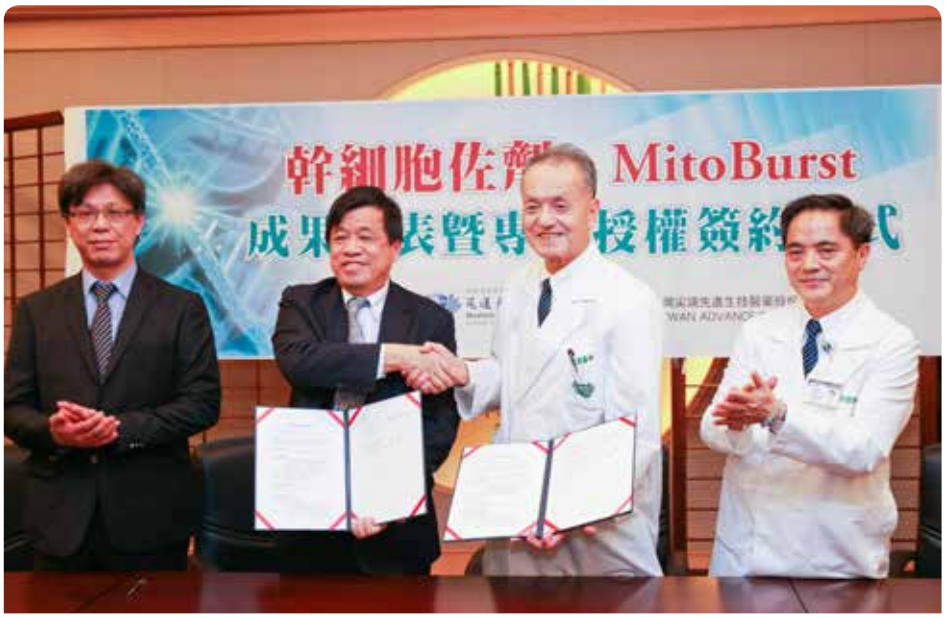
Fountain of Innovation

aims to discharge knowledge,
ripple inspiration,
infuse new ideas into the vast
and sublime world of medicine

The Stem Cell Adjuvant MitoBurst

Hoping to Activate Cure

By Huang Szu-Chi, Dr. Sun Li-Yi, Dr. Pang Cheng-Yoong, Dir. Cheng Ching-Feng of the Research Dept, Hualien Tzu Chi Hospital



Buddhist Tzu Chi Medical Foundation CEO Lin Chin-Lon (2nd right), Hualien Tzu Chi Hospital Supt. Lin Shinn-Zong (right), and Taiwan Advance Bio-Pharmaceutical Inc. Chairman Su Wen-Lung (2nd left) signed the patient licensing agreement.

Stem cells, characterized by the renewing and repairing of tissues and organs, have shed light on potential treatments for incurable diseases. But for stem cells to be therapeutic, it is essential to obtain "the right stem cells that are adequate in quality and quantity". Hualien Tzu Chi Hospital recently declared the completion of the mesenchymal stem cell culture system—stem cell adjuvant MitoBurst—that has obtained patents in many countries and is a potential solution to the aforementioned problems. The adjuvant is the result of a three-year research by Dr. Sun Li-Yi, Director Cheng Ching-Feng, and Deputy Director Pang Cheng-Yoong of the Department of Medical Research, Hualien Tzu Chi Hospital. The team began stem cell research in 2005 to tackle incurable diseases. Over a decade long endeavor was eventually rewarded with significant results in the pinpoint. The newly developed stem cell adjuvant MitoBurst is an advance on technology that cultivates functionally superior stem cells in reduced time, so that patients will not have to wait in vain.

On Dec. 12, 2016, Buddhist Tzu Chi Medical Foundation and Taiwan Advance Bio-Pharmaceutical Inc. (hereinafter referred to as Advance Pharma), represented by CEO Lin Chin-Lon and Chairman Su Wen-Lung

respectively, signed a patent licensing agreement, bringing hope to patients in need by integrating advanced medical research and industry experience.

Dr. Sun Li-Yi from the Department of Research elaborated on the stem cell research that, in the case of cerebral hemorrhage, according to clinical trials and animal studies, a treatment would require 100 million functional stem cells; a treatment for cirrhosis would require 200 million, and diabetes would most likely require 10 billion or more. The research team of Hualien Tzu Chi Hospital has been focusing on the cultivation of mesenchymal stem cells from fat tissues or umbilical cords, and the addition of MitoBurst to cultivate sufficient numbers of highly functional cells. In short, the technology reduces the working time of the culture process. Furthermore, the use of human autologous serum in cell culture can prevent contamination and infection when using animal serum, and enhances the differentiation potential of mesenchymal stem cells and the secretion of cell growth hormone, which translates to better treatment efficacy.

The presentation of stem cell adjuvant MitoBurst and the signing ceremony and its patient licensing agreement, a group photo of the staff and guests.

Stem cell therapy can have a wide range of medical application, with the precondition that there are sufficient quantities of quality stem cells. The properties of stem cells are influenced by source gender, health status, extraction methods, and culture methods. Dr. Sun Li-Yi explained that, in general, mesenchymal stem cells require 24 hours to 48 hours to begin cell division, and a set amount of time is needed to cultivate sufficient cell numbers. MitoBurst can reduce 1/3 or even 1/2 of the culture time. The saved time may be the difference between success and failure. Take hemorrhagic stroke for example, it is almost inevitable that patients, after stabilized, to suffer from the sequelae of brain injury, and there are no effective conventional therapy in the discipline of medicine aside from long-term rehabilitation. The emergence of stem cell therapy will most likely serve as an alternative to these patients.

Tzu Chi Medical Foundation CEO Lin Chin-Lon indicated that the application of hematopoietic stem cell transplantation in hematological diseases is the most common use of stem cell therapy. The applications of other stem cells in tissue and organ regenerations are still in clinical trials. Hualien Tzu Chi Hospital is currently investigating, and with some promising results, the application of mesenchymal stem cell therapy on hemorrhagic stroke, optic nerve trauma, and wound healing. It is hoped that via the collaboration between the research team and the medical team, the research can advance to human trials, and eventually applied in clinical treatment. Chairman Su Wen-Lung said that Advance Pharma has been rooted in medical biotechnology ever since its founding, and in addition to specializing in food safety diagnostic kits for aquatic, livestock, and agricultural products, the company is actively investing in drug development; in terms of technology associated with stem cell proliferation, the company has obtained patents in China, Singapore, Taiwan, Russia, Japan, America, Korea, and EU. Advance Pharma is glad to collaborate with Buddhist Tzu Chi Medical Foundation, Chairman Su added, and he believes that together they can develop effective stem cell therapeutic products to treat rare and incurable diseases, and position Taiwan as the international leader in stem cell therapy.

The discipline of stem cell and cell therapy prospered in the recent years. There are currently 679 clinical trials of mesenchymal stem cells in progress worldwide (Taiwan has 13), and Canada, Japan, and

Dr. Sun Li-Yi explains that mesenchymal stem cells are pluripotent.

Korea have newly approved stem cell drugs that target cardiac and cerebrovascular diseases, knee degeneration, intestinal diseases and reduction of cell transplantation risks. “Save your own organs,” Supt. Lin Shinn-Zong asserted. He pointed out that autologous fat tissue is easily accessible, with MitoBurst, mesenchymal stem cells of fat tissue can be cultivated from autologous serum, avoiding heterogeneous contamination and ethical concerns associated with culture using heterologous serum.

The first inventor Dr. Sun Li-Yi explained that mitochondria inside mesenchymal stem cells, nicknamed the “electric generator”, is the key to enhancing the quality and quantity of stem cells. MitoBurst is a unique culture method that activates mitochondria in mesenchymal stem cells using antioxidant under normoxic conditions. The operating mechanism is similar to hypoxia culture, a method that has been mentioned in thousands of published articles. Hypoxia culture is a method that regulates cell cycle progression by inhibiting the expression of a p21, and preserves the multi-potency of mesenchymal stem cells as cell number continues to grow. The amount to time taken to grow a sufficient quantity of stem cells is closely related to the short span of time available in life-saving emergencies and the reduction of production cost. Although MitoBurst appears to be just another culture method, it is in fact a technological breakthrough longed by physicians and industries in the field.

Not only is MitoBurst simpler and cheaper than the aforementioned hypoxia culture, it overcomes the slow cell growth

of mesenchymal stem cells cultured in human serum. Animal cell culture, majority of the labs in the world uses fetal bovine serum as an essential ingredient of culture media. Although reports have confirmed that the said culture method will not lead to cell cancerization, it still carries the risk of contamination from fetal bovine spongiform encephalopathy, commonly known as mad cow disease.

The research team of Hualien Tzu Chi Hospital discovered that cells from the same human donor cultured in fetal bovine serum or human serum respectively are different in appearance and in the expression of cell surface antigens. Scientifically speaking, it is hard to say that the cells cultured in two different serums as one and the same. Moreover, the use of fetal bovine serum is based on the sacrifice of animals. To reduce or even avoid animal sacrifice, the team explored a new possibility in an attempt to develop a safe and effective treatment, by replacing fetal bovine serum culture with human serum culture extracted from the donors in all mesenchymal stem cell researches.

Hualien Tzu Chi Hospital has been applying human mesenchymal stem cells cultivated by MitoBurst in hemorrhagic stroke, optic nerve trauma, wound healing, and organ failures, and the effort has yielded

The three inventors behind the successful development of MitoBurst, starting from the left, are Dr. Sun Li-Yi, Dir. Cheng Ching-Feng, and Deputy Dir. Pang Cheng-Yoong.

significant results. Apart from publishing relevant results on international journals, the team will prioritize and advance researches that yielded the best result to clinical trial.

The core member of the research team, Dir. Cheng Ching-Feng, indicated that Hualien Tzu Chi Hospital set up Epidemiology and Biostatistics Consulting Center, Clinical Trial Center, Institute of Eye Research, Laboratory Animal Research Center, and Tzu Chi Biobank to increase the depth and breadth of their research. Also a pediatric cardiologist, Dr. Cheng Ching-Feng assumed the director position at Department of Medical Research in 2010, and has been ever since actively training researchers, facilitating translation of researches, assist physicians in clinical research, hold regular courses on statistical consultations relevant in epidemiology, and design practical lab courses for physician-scientists. On top of that, he hired several full-time researches with doctoral degrees in charge of core labs and case study rooms. He also drafted criteria similar to Academia Sinica on researcher promotion and assessment.

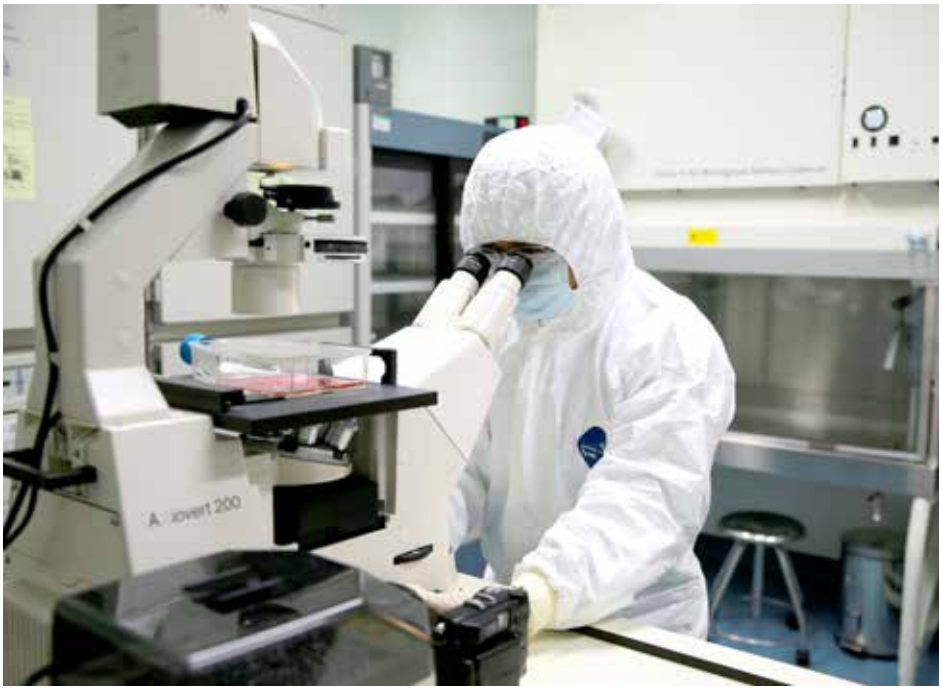
MitoBurst first inventor Dr. Sun Li-Yi was recruited by Dir. Cheng in 2011 as a postdoctoral researcher into the Department. Due to his outstanding performance, Dr. Sun was promoted to research assistant in two years, and later placed in charge of research work at GMP standard Gene and Stem Cell Production Laboratory.

Deputy Dir. Pang Cheng-Yoong, one of the inventors, pointed out that Master Cheng Yen built Hualien Tzu Chi Hospital because of the destitute of medical resources in eastern Taiwan. The Hospital, which has been upgraded to a medical center since, continues to struggle against incurable diseases like neurodegenerative diseases (including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, dementia, etc.), cardiac and cerebrovascular injuries (including heart disease, intracranial hemorrhage, stroke, etc.), and various cancers. After Supt. Lin Shinn-Zong laid a foundation for stem cell therapy 15 years ago, his successors—teams from Department of Medical Research and Neuro-Medical Science Center—continue to develop new treatments targeting brain damage and Parkinson's disease.

A new drug using Urocortin to treat brain injury and Parkinson's

disease and MitoBurst are some of the recent achievements. Urocortin, a drug that can effectively inhibit brain injury induced ncreased intracranial pressure, cerebral edema and neuritis, has obtained a patent in the United States, and Dr. Liew Hock-Kean from the Department is in charge of formulation development and pharmacokinetic study. On the other hand, Urocortin is proven to protect and promote midbrain dopaminergic neurons, and the inventor Dr. Wang Mei-Jen is in charge of the drug efficacy testing on Parkinson's disease. Patent applications for the new drug have been filed in Taiwan and in the United States, and both are currently under review.

As for MitoBurst, the mesenchymal stem cell culture platform, Hualien Tzu Chi Hospital has transferred this technology to Advance Pharma, where it will provide mesenchymal stem cells storage service, and continues to collaborate with Hualien Tzu Chi Hospital on related clinical trial development. It is the hope of both parties to one day apply their research in clinical treatments and benefit patients with battling against rare or incurable diseases.



The researchers are conducting experiments on the stem cell adjuvant. The pink liquid in the petri dish is MitoBurst.