Shengbiao

CREATING HIGH-QUALITY MEDICAL PRODUCTS

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As China works to become an undeniable world leader in science and technology, boosting biomedical innovation has been a big part of the government's agenda. An ambition to reduce China's dependence on imports by developing high-quality local biomedical products led to the founding of Shengbiao (Shanghai) Medical Equipment Technology in 2016.

Shengbiao Medical focuses on medical device technologies and provides pilot testing of biomedical products. It plays an essential role in the translation of research into new technologies and commercial products, filling an important gap in the biomedical industry.

Within a year of its founding, Shengbiao Medical established a subsidiary company, Sun-Bio Medical Device, in Japan. It focuses on the development and sales of innovative medical technologies and products, including a novel bispecific antibody that combats lung cancer.

"Unlike most biotech companies that simply gather a group of employees for research and development (R&D), we are a resource-based development platform that leverages corporate players in the biomedical field," said Siwei Jiang, the chairman of the board of Sun-Bio Medical Device and Shengbiao Medical. "We complement other enterprises in the Chinese biomedical industry by linking research institutes and corporate partners to bring research innovation to the global market."

A pragmatic approach to development through attracting talent is the core philosophy of Shengbiao Medical and its subsidiary, Sun-Bio Medical Device. The company emphasizes the authenticity, feasibility, potential and the sustainability of projects to minimize the risk to its investment. "We want to initiate a new round of high demand for quality medical devices on the market, which will bring profit growth," said Jiang. "And a sustainable product that is likely to be a blockbuster will also attract talent, making you grow stronger."

RAPID RISE OF A BIOMEDICAL TECHNOLOGY PROVIDER

The development of Shengbiao Medical and Sun-Bio Medical Device has been fast. The latter has already filed several patent applications, including one in the United States and one in Europe. It also already holds a patent on a means of fluorescence-based precancerous lesion diagnosis.

While phototherapy and diagnostic imaging technologies are at its core, Shengbiao Medical has now also ventured into drug innovation, particularly, molecular targeted therapies for cancer. Careful screening by Sun-Bio Medical Device's research team using recombinant DNA techniques has led to the discovery of a bispecific antibody for lung cancer, called YY0411. This antibody targets two cancer driver genes at the same time and offers an effective medical approach to improve lung cancer treatment and prognosis. Sun-Bio Medical Device has filed a patent registration for its bispecific antibody, and the results from pre-clinical studies have been published in quality medical journals.

FIRST-RATE THINK TANK VIA PARTNERING

As a resource platform, fostering quality partnerships is integral to Shengbiao Medical's development. It has established collaborations with the world's leading industrial players and is developing collaborations with overseas research institutions and hospitals for future R&D and clinical trials.

Meanwhile, strong ties are also being forged with local hospitals and research institutions. For example, for R&D and clinical trials of its novel drugs, a strong partnership has been built with the Shanghai Pulmonary Hospital, which is affiliated with Tongji University medical school.

Shengbiao Medical is also keen to strengthen its research capacities through developing a network of extraordinary talent. Together with its subsidiary in Japan, Sun-Bio Medical Device, it has gathered an international team of experts, including Diego Gonzales Rivas, a thoracic surgeon at Coruña University Hospital, Meinoshin Okumura, a lung cancer surgery expert from Osaka University, Gaetano Rocco, chief of the Division of Thoracic Surgery at the National Cancer Institute of Pascale Foundation in Italy, and Harvey Pass from the New York University's School of Medicine, in addition to a wealth of talent within the ranks of its local partners. With industrial leaders, experts, scholars and government authorities working together through the platform, Sun-Bio Medical Device has set out to lead the field of medical applications with its research innovations.

GIVING BACK TO SOCIETY

Shengbiao Medical puts social responsibility at the top of its agenda, and it aims to improve social wellbeing through its innovations. While many of its inventions or technologies are still in the process of clinical trials, they have great potential to improve community wellbeing.

Giving back to society is part of Shengbiao Medical's remit and it is actively building public welfare platforms. Several public service programmes are being planned, including a fellowship programme to sponsor 'Shengbiao Scholars' in local universities to nurture young talent.

Shengbiao Medical has an 'open innovation' mindset and adheres to international standards to build high-end medical products. By optimizing its management systems and business operations mechanisms, leveraging their own resources and those of their partners, and working with industry experts, Shengbiao Medical is poised to advance its resource-based R&D platform to bigger and better things. ■

AN EXTENSIVE NETWORK OF INTERNATIONAL EXPERTS

Shengbiao Medical and its subsidiary, Sun-Bio Medical Device, have brought in a group of international experts to be project members for its R&D of the bispecific antibody, YY0411.

DIEGO GONZALEZ RIVAS, MD

DIRECTOR of the uniportal VATS training program, Shanghai Pulmonary Hospital, Tongji University, China

DIRECTOR of the International innovative drug research clinical base, Sun-Bio Medical Device

GAETANO ROCCO, MD

CHIEF Division of Thoracic Surgery, National Cancer Institute, Pascale Foundation, Italy

HEAD Department of Thoracic Surgery and Oncology, National Cancer Institute, Pascale Foundation, Italy

HARVEY PASS, MD

PROFESSOR Department of Surgery, New York University Langone Medical Center, USA

PROFESSOR and **VICE CHAIR** for Research, Department of Cardiothoracic Surgery, New York University Langone Medical Center, USA

MEINOSHIN OKUMURA, MD

PROFESSOR Department of General Thoracic Surgery, Graduate School of Medicine, Osaka University, Japan

PRESIDENT elect of 36th annual conference of Japanese Association for Chest Surgery (JACS)

DOUBLE TROUBLE FOR LUNG CANCER

Molecular biology studies have unearthed a fresh bispecific antibody, YY0411, which has an effective two-pronged attack on our most deadly cancer.

More people die from lung cancer than any other cancer. It was responsible for 1.69 million deaths in 2015, according to the World Health Organization, and it is a growing problem for China. Finding ways to combat the disease is one of the main objectives of the R&D team at Sun-Bio Medical Device based in Tokyo, Japan. Recently, they developed a bispecific antibody that blocks two lung-cancer cell signalling components with researchers at Shanghai Pulmonary Hospital, an affiliate of Tongji University. Pre-clinical tests already suggest promising responses from early- and advanced-stage patients.

GROWING CHINESE LUNG CANCER ISSUE

During the past 10–15 years, the number of people in China affected by lung cancer has been on the rise. The latest government estimates suggest that there were 730,000 new Chinese lung cancer cases in 2015, accounting for 36 percent of the world's total lung cancer cases that year, and 17 percent of the nearly 4.3 million new cancer cases across the country.

"Studies have shown that smoking-driven lung cancer has been decreasing," says Yang Yang, one of the lead scientists on the Sun-Bio Medical Device study. It is suspected that the country's devastating air pollution problem is responsible for an overall rise in lung cancer incidence, particularly as new cases are arising from populations less likely to be smoking, such as women and children. Though five-year survival rates are increasing with improving treatment techniques, the rising number of incidences and huge number of deaths have led to a strong demand for effective lung cancer therapies.

"The dysregulation of cell signalling pathways, which leads to cell proliferation, is the main cause of lung cancer," explains Yang. Molecular biologists, he says, have already shown that lung cancer tumours have high heterogeneity, meaning that each patient's lesions are unique and require personalized treatment plans. Identifying specific targets relevant to an individual's cell signalling dysfunction is the most difficult part of the job, he says.

The bispecific antibody, YY0411, targets two driver genes of lung cancer, presenting improved effectiveness in killing cancer cells.

WEI YIN

ASSOCIATE PROFESSOR
Institute for Advanced Study, Wuhan University

"An antibody like this has never been explored before."

> **The treatment of lung cancer is advancing rapidly these days. Thirty years ago, less-invasive surgeries were not an option, while now we are performing video-assisted thoracoscopic surgery called VATS, reducing patient pain while increasing their chance of survival.**
>
> **At the same time, medical oncology is making big progress. With the discovery of YY0411, lung cancer patients will enjoy a strong possibility of survival ... This is really the first bispecific antibody targeting two different molecules — HER2 and VEGF. This new kind of antibody will dramatically improve the outcome of lung cancer treatments. I hope the number of patients surviving lung cancer will increase dramatically.**

— Meinoshin Okumura, Osaka University Graduate School of Medicine

EAST ASIA'S GUILTY GENES

To locate cancer targets and genes relevant to Asian populations, the researchers first analysed large samples of data. "The first question we asked was: 'What are the phenotypic characteristics for lung cancer patients in East Asia?'" says Yang. "Then, to determine our treatment targets, we asked: 'What are the common cancerous driver genes for this population?'"

A study of the symptoms and pathology of 1,033 Chinese lung cancer patients showed that the majority were still within 'stage I', based on a measure known as the Tumour, Nodes and Metastasis (TNM) staging system. The system looks at tumour size, the number of cancerous lymph nodes, and the development of secondary cancers at a distance from the primary cancer (metastasis). More than half of the patients, adds Yang, have tumours between 11 and 30mm.

The researchers also screened 10,461 patients from Shanghai Pulmonary Hospital for the genes driving their lung cancers. The results suggested that 73 percent have adenocarcinoma, malignant tumours formed from glandular structures in epithelial tissue, followed by nearly 15 percent with squamous cell carcinoma, a cancer that starts in the flat cells lining the inside of the lung's airways.

One of the major drivers of the disease was found to be the gene for the human epidermal growth factor receptor 2 (HER2). Over-expression of HER2 was detected among 30 percent of the studied patients and in 59 percent of stage II and stage III patients. Furthermore, an overactive HER2 signalling pathway was found in 72 percent of lung cancer patients, and this percentage increases with the progression of disease lesions.

While HER2 is typically found to contribute to the development of breast cancer, it is also closely related to the progression of ovarian cancer and lung cancer. However, not many lung cancer drugs target the HER2 gene, says Yang. Yet, previous studies have found poor survival rates in cancer patients with HER2 mutations, compared with those that have other gene mutations, meaning that there is an urgent need to develop HER2-targeted therapies. "HER2 plays a critical role in cell proliferation, survival and invasion," Yang says. "Cancers with high expression of HER2 are

YANG YANG

ASSOCIATE PROFESSOR
Shanghai Pulmonary Hospital, Tongji University

> As a thoracic surgeon, I see lung cancer patients on a daily basis. While resection surgery provides the most effective treatment to date, there is still the chance of relapse. There are also patients who are not suitable for surgery. Thus, I'm keen to find a non-surgical treatment to effectively control the disease and alleviate patients' pain.
>
> The major difficulty in cancer drug development now is finding the right treatment targets. It is after lots of tedious analyses that we have located HER2 and VEGF as targets and developed an antibody aimed at both. The large patient base and excellent surgical expertise of Shanghai Pulmonary Hospital provide a solid foundation for the R&D of targeted lung cancer therapy. Now Sun-Bio Medical Device will be in charge of further testing of YY0411 to turn it into a therapeutic product. We are excited about the effectiveness of our bispecific antibody for lung cancer treatment.

highly likely to develop metastasis and have poor sensitivity to chemotherapy."

Expression of vascular endothelial growth factor (VEGF), a protein that stimulates angiogenesis, namely, the growth of new blood vessels, was also detected in 60 percent of screened patients. In addition, 80 percent of the lung cancer patients were found to have an over-active VEGF signalling pathway. VEGF is usually associated with a variety of cancers, as blood vessels send in nutrients that cancer cells need for growth. Targeting VEGF to inhibit angiogenesis can block the nutrition supply to cancer cells and limit the progression and metastasis of cancer. "So, our goal was to develop a bispecific antibody that simultaneously targets both HER2 and VEGF," says Wei Yin, another scientist on the project. "An antibody like this has never been explored before."

MORE TARGETED TREATMENTS

Current treatments for lung cancer normally rely on either resection or chemotherapy, depending on the pathological stage of the tumours. While surgery to remove the tumour is usually the best choice for early stage patients, there is a risk of local recurrence or spread to other tissues or organs. Chemotherapy is typically applied to patients in advanced stages and it is usually accompanied with serious side-effects and frequently fails due to patients who exhibit drug resistance.

Monoclonal antibody therapy – the use of artificially produced molecules as substitute antibodies to bind to cancer cells – is a type of immunotherapy that triggers the immune system to attack cancer cells. Because it is more targeted than chemotherapy's attack on both cancerous and healthy cells, it may work more efficiently and have less severe side effects.

The US Food and Drug Administration (FDA) has already approved the use of several monoclonal antibodies for cancer treatments, which have been released under the names Avastin, targeting VEGF, and Herceptin, which inhibits HER2. However, Herceptin is typically used for the treatment of early-stage breast cancer and its clinical use is limited, as HER2-positive patients frequently develop Herceptin resistance. Patients using Avastin, usually for the treatment of metastatic colorectal cancer, also risk haemorrhage and gastrointestinal perforation – meaning targeted and effectual use is key.

On the other hand, bispecific antibodies, with dual specificity, can simultaneously interact with a target tumour cell and a functional cell, usually a T cell, and thus, may kill cancer cells more effectively. In fact, it has been shown that they are 100–1,000 times more effective than monoclonal antibodies, and can achieve equivalent effects with a much lower dosage than monoclonal antibodies, giving it a competitive edge in both potency and price. Thus, bispecific antibodies are now considered the next-generation in antibody treatments for cancer.

In search of a more effective treatment for lung cancer, R&D staff at Sun-Bio Medical Device constructed 160 combinations of HER2 and VEGF molecules using recombinant DNA technology. After careful screening of candidate molecules, they selected the most targeted and specific, a novel bispecific antibody they called YY0411.

"Our analyses suggest that YY0411 presents higher efficiency in recognizing and blocking HER2 and VEGF than using commercially available HER2 and VEGF monoclonal antibodies alone or together," says Yang. "YY0411 also binds better to HER2 and VEGF."

Furthermore, studies to verify the biological functions of YY0411 show that this bispecific antibody blocks HER2- and VEGF-mediated signalling pathways, and thus inhibits lung cancer cells from proliferating and generating tumours. "It is evident that YY0411 performs better than commercially available HER2 and VEGF monoclonal antibodies," Yang says, "whether they are used alone or in combination."

PROSPECTS FOR CLINICAL USE

Pre-clinical studies suggest that both early- and advanced-stage lung cancer patients may benefit from the bispecific antibody, YY0411. For those with early stage lesions, doctors can apply YY0411 to patients with HER2 and/or VEGF over-expression after determining the cancer's genotype and expression levels through analysis of resected cancer tissues using real-time polymerase chain reaction. This individualized treatment could prolong the progression-free survival period. As for patients with advanced stage lesions, YY0411 has the potential to improve survival by effectively blocking both HER2 and VEGF, and inhibiting the tumour progression.

While further work has to be done before this antibody reaches the market, the researchers are enthusiastic about the impact their work could have on many lung cancer sufferers. "We are excited about the potential of YY0411 as a powerful anti-cancer therapy," says Yang. "Coming next – we will further analyse [the antibody's] toxicological properties to provide more robust scientific evidence for further clinical trials, and we will explore its use in treating other cancers." ■

Shengbiao

Reading fluorescent signals to shed light on cancer prevention

A testing device that uses intrinsic fluorescence to detect precancerous cervical lesions and early-stage cervical cancer has been developed at Shengbiao (Shanghai) Medical Equipment Technology, providing an effective tool for improved prevention and treatment.

Cervical cancer is a common gynaecological disease, accounting for 10% of all gynaecological tumours. While effective prevention and control approaches are available, it still led to 270,000 deaths worldwide in 2015, the majority occurring in less developed regions, where effective screening is lacking. "Effective, rapid and efficient screening technologies will significantly reduce the risk of cervical cancer," said Bogen Song, general manager of Shengbiao Medical and a pathology professor from Tongji University.

Fluorescence, the emitted light from a substance, is widely used in biochemical and medical research for analysing organic compounds. It has been an established screening tool for precancerous lesions and cancer detection in clinical settings since 1980s, according to Song.

Many proteins contain intrinsic chromophores that can emit light once excited, making it possible to image proteins or molecules in human body cells without the use of any fluorescent chemicals. Shengbiao Medical's invention is based on this intrinsic fluorescence imaging technology.

Developing excitation light and capturing intrinsic fluorescent signals are the major technical difficulties, explained Song.

Shengbiao Medical's device uses an ultraviolet light beam at a wavelength of 340nm, instead of nitrogen molecular lasers, to improve excitation light. It excites electrons in the protein molecules of cervical tissues, which emit intrinsic fluorescence. Molecular structural changes of proteins in cancerous cells and tissues mark them as different from proteins in healthy ones, meaning they send different fluorescent signals. Analysing these can reveal abnormalities in cervical tissues.

However, the difference in fluorescence may not be very marked and the signals can be short-lived. Shengbiao Medical's solution is to sharpen the grayscale images to enhance the differences. By converting fluorescence images into black-and-white, the device captures and fixes intrinsic fluorescence signals, enabling clearer images. These provide gynaecologists with more detailed information, assuring more accurate diagnosis.

The effectiveness of the technology has been proven in clinical studies. The detection and accuracy rates in diagnosing precancerous cervical lesions and early signs of cervical cancer are both higher than 90%. The device can also be used for colposcopies, allowing more convenient cervix checks.

The diagnostic device developed by Shengbiao Medical recently passed the China Food and Drug Administration safety test and was approved for larger-scale clinical trials. It is expected to be put into clinical use soon, enabling early detection and more effective treatment of cervical diseases. ■

Shengbiao Medical's device sharpens the grayscale images of cells and tissues to enhance differences in fluorescence signals.

JIANHUA LIU

CHAIRMAN
Department of Obstetrics & Gynecology,
Shanghai Ninth People's Hospital,
Shanghai Jiaotong University
School of Medicine

"Early diagnosis and treatment are crucial for improving tumour therapy success. Autofluorescence imaging reveals the growth of cancerous or precancerous lesions by comparing the differences between normal and diseased tissues, offering a highly sensitive tool for early diagnosis of high-grade intraepithelial neoplasia and early-stage cervical cancer. Shengbiao Medical's device presents high potential for improving women's health. Next, we will improve the imaging by spectroscopy for more objective and effective diagnosis and seek applications in hysteroscopy, endoscopy and beyond."

Clinical prospects of intrinsic fluorescence

Cancer is one of the leading causes of death worldwide, but if detected early, many cancers are now treatable. Advances in imaging technologies have significantly improved the chances of early cancer diagnosis. An example is the recent development of a fluorescent diagnostic device at Shengbiao Medical Equipment Technology, which has shed light on the improved diagnosis and treatment of cervical cancer.

Here, **Gening Jiang**, chief of the Department of Thoracic Surgery at Shanghai Pulmonary Hospital of Tongji University and chairman of Shanghai Society of Thoracic Surgery,, discusses autofluorescence imaging technology and its use in precancerous lesion detection beyond cervical cancer.

Q: How do you define the significance of the autofluorescence imaging technology developed at Shengbiao Medical?

All over the world the incidence of cancer is rapidly increasing. In China, among the most prevalent are lung, gastric and colorectal cancers, all of which have high fatality rates, as they are usually in advanced stages when diagnosed, limiting the use of surgery and other effective treatment options. Indeed, the most effective way to improve cancer treatment success is early diagnosis. For instance, the five-year survival rate of gastric cancer reaches more than 90% when detected early. However, precancerous lesions developed in mucosal organisms are very similar to benign changes, making them hard to detect.

Using intrinsic fluorescence, the probing device developed at Shengbiao Medical enables real-time diagnosis of precancerous lesions and improves the accuracy of diagnosis. It is applicable to the early detection of cervical cancer, a high-incidence tumour for women, as well as other prevalent cancers, such as lung cancer, with great potential for improving cancer prevention and treatment.

Q: How can autofluorescence imaging be used for diagnosis?

There are two major approaches for using intrinsic fluorescence for diagnosis. One is to use light of a certain wavelength to excite tested organisms to emit intrinsic fluorescence. The fluorescent images will then be turned into black-and-white grayscale images to show the lesioned areas and define their borders more clearly. Another way is to transform the fluorescence signals into spectra using an oscilloscope or a magnification system. Analysis of emission spectra peak will reveal distinctions between normal and cancerous tissues.

> **"Indeed, the most effective way to improve cancer treatment success is early diagnosis."**

Q: What is the current use of Shengbiao Medical's fluorescence diagnostic instrument?

The fluorescence diagnostic device is currently targeted at detecting cervical cancer. It is more effective than colposcopy, which typically uses an external white light source to magnify the vagina and cervical areas to 10-40 times their normal size to detect lesions and take biopsy samples. Shengbiao Medical's device does not simply rely on detecting the morphological changes of lesions, but also makes a diagnosis based on the different molecular structures of cancer cells, which send different fluorescence signals. It enables distinguishing cancerous and inflammatory lesions in real-time and is less invasive. Used in tandem with colposcopies, the technology will improve the efficiency of regular cervical checks.

Q: What are potential applications of the technology?

One direction for future research is to use the autofluorescence imaging technology in endoscopies to screen for precancerous lesions in the digestive tract. Normal endoscopes make cancer diagnosis based on biopsy results and morphological changes in tissues, and may not be as good at detecting precancerous or early-stage lesions. Using a special optical fibre, light of a specified wavelength can be sent in through the endoscope to excite intrinsic fluorescence from the tissue being examined. The signals will be sent back and displayed in spectra for real-time diagnosis. Moreover, the technique is applicable for examinations of intestinal, tracheal and bronchial mucosa for precancerous lesions. I'm also looking forward to its application in lung cancer diagnosis. It will be a useful tool for clinicians. ■