THE PATH TO PERSONALIZED CANCER IMMUNOTHERAPY

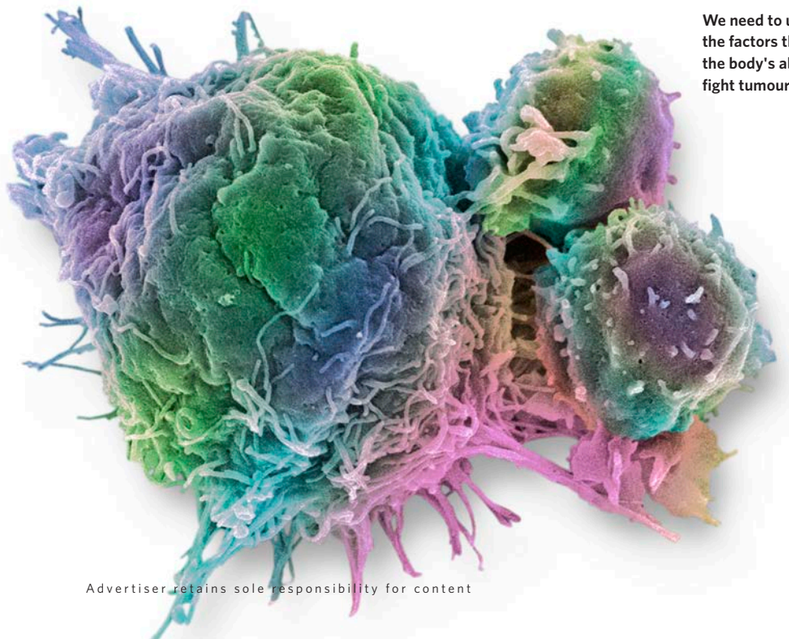
ADVANCES IN TUMOUR IMMUNOLOGY are enabling clinicians in China to provide increasingly tailored treatment for cancer patients.

In this Q&A, Dr Erwei Song, president of Sun Yat-sen Memorial Hospital in Guangzhou, China, outlines the hospital's research and clinical achievements in the field of tumour immunotherapy.

How could tumour immunotherapy have impact?
Tumours develop through a continuous dynamic interaction between cancer cells and the immune system. Stimulation of the immune system to help it fight cancer — immunotherapy — is one means of treating malignant tumours. In fact, the comprehensive assessment of the strength of an individual's anti-tumour immunity can help clinicians to judge the functional status of their immune cells and form a prognosis, predict recurrence risk and formulate precision treatment strategies. It can also help predict the risk of cancer in healthy people, aiding early diagnosis and treatment.

What are the main challenges in your field?
In recent years, the concept of 'hot and cold tumours' has been used to assess the strength of anti-tumour immunity. T-cell infiltrated 'hot' tumours are sensitive to immunotherapy and thus patients suffering from them are thought to have a better prognosis and survival rate. In contrast, it is generally believed that 'cold' tumours show little or no T-cell infiltration and are unlikely to be altered by immunotherapy. However, there is growing evidence that the T cells infiltrating tumours are mostly bystanders that do not kill tumour cells, while an alternative theory suggests natural killer (NK) cells — an immune cell that can kill foreign, infected or transformed cells — might be responsible for the improved prognosis of patients with hot tumours. But NK cells remain little understood. These factors limit the diagnosis and assessment of human anti-tumour immunity. Furthermore, anti-tumour immunity is an individualized and dynamic process, which varies among tumours, molecular types of the same tumour, and even the same patient at different stages of tumour treatment. In order to treat tumours, we need to know how to target patients accurately.

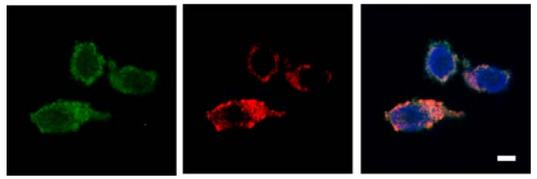
ERWEI SONG
President of Sun Yat-sen Memorial Hospital



We need to understand the factors that impact the body's ability to fight tumour cells.

Steve Gschmeissner/SPL/Getty

How are you helping to solve these problems?
In July 2022, I proposed the concept of Effector Immune Cell Deployment (EICD) as a way to understand tumour immunity, as part of a review published in *Trends in Immunology*[1]. EICD refers to the initiation, activation, circulation, recruitment, infiltration, and cell fate of effector immune cells in lymph nodes, peripheral blood, and tumour microenvironments, including T cells for adaptive immunity and NK cells for innate immunity. T cell-mediated adaptive immunity in the EICD model is thought to be due to genetic mutations of tumour cells and the production of tumour-specific antigens. However, some tumour cells can hide from T cells, and they are killed by natural immunity mediated by NK cells. Based on the complexity and diversity of tumour immune escape mechanisms, I propose to combine the multiple immune variables that regulate EICD to comprehensively evaluate anti-tumour immunity, and use multiple diagnostics, including molecular, cytology, histology, and imaging, to elucidate these subtleties.



▲ **Chemotherapy promotes the presence of FN-responsive nuclear factor-κB activator (green) and protein kinase R (red) in macrophages, and these increase the production of protumour inflammatory cytokines.**

What are some of your greatest successes in clinical treatment?
Professor Fengxi Su, an oncologist at the Sun Yat-sen Memorial Hospital, and I established the Department of Breast Surgery more than 20 years ago. Our team was among the first in China to carry out breast conserving surgery (BCS) for cancer patients in the early 1990s. The hospital also offers precision treatment for early and advanced breast cancer, and we can predict patient recurrence risk. The five-year survival rate of Sun Yat-sen Memorial Hospital patients exceeds 92.5%, which is in line with leading international institutions.

Our team has also taken the lead in proposing that after breast-conserving surgery for breast cancer, tumour treatment can be improved by modulating the tumour microenvironment. For instance, in an 2021 *Nature Cancer* publication[2], my team explained that although adjuvant chemotherapy can stimulate antitumour immunity by inducing the interferon response, which is when a virus-infected cell releases interferons, causing nearby cells to heighten their anti-viral defences, it can also activate the production of protumour inflammatory cytokines in macrophages. Targeting this process is an effective therapeutic strategy to reverse tumour-promoting inflammation.

What brought you to the study of tumour immunology?
After completing a seven-year clinical medicine programme at Sun Yat-sen University in 1995, I became a general surgeon here, specializing in tumours. It then became my goal to conquer malignant tumours. From 1999 to 2004, I studied transplantation immunity at the University of Essen, in Germany, and did postdoctoral research at the CBR Institute for Biomedical Research at Harvard Medical School, specializing in viral immunity. During those years, I embarked on a journey to explore the clinical application of RNA interference, which is a response to double-stranded RNA that mediates resistance to both internal parasites and the DNA or RNA from a virus, and regulates the expression of protein-coding genes. After returning to China, I turned my research toward RNA interference in the treatment of breast cancer, as most advanced topics in the field of oncology start with breast cancer due to its high incidence. In 2019, I was elected as Member of the Chinese Academy of Sciences, the first in the field of breast surgery in China.

CHINA'S LEADING CLINICAL TREATMENT AND RESEARCH HOSPITAL

Sun Yat-sen Memorial Hospital in Guangzhou was founded in 1835, and is part of Sun Yat-sen University, named after Dr. Sun Yat-sen, the first provisional president of the People's Republic of China, who studied medicine there. It is thought to have been the first school and hospital of Western medicine in China, and the site for many of China's first medical innovations, such as eye surgeries, amputations, bladder lithotomies, use of ether and chloroform anaesthesia and medical X-rays. The hospital now specialises in seven national key disciplines: internal medicine (nephrology, endocrine and metabolic diseases), surgery, neurology, oncology, otolaryngology and ophthalmology, and is also equipped for heart, lung, liver and kidney organ transplantation. The hospital is oriented towards clinical research and is focused on generating insights that can be transformed into clinical practice. As a result, it runs a national project to improve the diagnosis capacity and treatment of critical diseases in oncology. It also reached 187 authorized patents in 2021, with 11 making it to market, including a urine RNA-based bladder cancer prediction kit and a means of doing orthopaedic surgery using thoracolumbar intervertebral space formers. It was ranked 18th in the world among academic institutions by the Nature Index in 2022.

What is the hospital's plan for future research?
We will continue to examine tumour immunity's regulatory mechanisms through the EICD model. We also hope to form a precise diagnosis method based on the immune-system for malignant tumours. And we will continue to screen for new potential therapeutic targets and work on ways to turn cold tumours into hot tumours. ■

REFERENCES

1. Zhang, J. *et al. Trends Immunol* (2022)
2. Liu, J. *et al. Nat Cancer* (2021)

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