Chasing on the way of cancer immunotherapy

I would like to share my experience of research in the following story. Based on my background regarding multiple directions in the field of cancer research including antiangiogenesis therapy, specific inhibitors of cancer cell repopulation between cycles of chemotherapy, and immunotherapy, I personally think the most promising approach to cure cancer might be through modulation of the immune system based on my research experience in past two decades.

After graduating from Shandong Medical School in 1980s, I started doing cancer research at the Experimental Oncology Laboratory, Shandong Academy of Medical Sciences, China. At that time there was a fascinating hypothesis "*Starving tumors by terminating their blood supply*" initially proposed by Dr. Folkman from Harvard Medical School. I chased after this novel concept for many years and attempted to demonstrate this hypothesis in our animal tumor models. We established a methodology to screen candidate angiogenesis inhibitors (AI) using the chick embryonic chorioallantoic membrane (CAM) assay, including development from avascular to vascular stages during the early development of chick embryos. In such way, a wide variety of agents were tested, and we successfully developed several AI. Based on our previous studies, anti-angiogenesis therapy was believed to work well to fight against some malignant solid tumors, especially lung, breast and esophageal cancers and also to be effective to cure benign hemangioma. One of the most promising angiogenesis inhibitor, AI-6, was even tested in clinical trials at the Affiliated Tumor Hospital of Shandong Academy of Medical Sciences. The combined therapy of anti-angiogenesis therapy with conventional therapy including surgery, chemotherapy or radiotherapy was demonstrated to have improved efficacy in our clinical trials. However, the trials also showed limited efficacy and relapse could eventually occur, suggesting failure of such a strategy to fight against cancers.

The human steps to fight against cancers would never stop. Since then, we kept searching for new and practical approaches to the treatment against cancers. One day, I accidentally noticed a publication of research paper by Dr. Tannock from Princess Margaret Hospital/Ontario Cancer Institute (PMH/OCI), University of Toronto, Canada. In this paper, the authors reported that cancer cell repopulation during the intervals of treatments with chemoradiation is a neglected area by scientific research, which is most likely to cause treatment failure. This idea was inspiring to me and I contacted him immediately by emails to show my interests. Luckily, Dr. Tannock then provided me an open position in his laboratory as a postdoctoral fellow and a good salary to study cancer cell repopulation between cycles of chemotherapy in mouse models.

Dr. Tannock is the pioneer in the research field of cancer cell repopulation between cycles of chemotherapy. During my postdoc period, we demonstrated that cancer cell repopulation between cycles of chemotherapy speeds up and this process can be suppressed by specific inhibitors. Cancer cell repopulation during the intervals of treatments has been considered an important factor of treatment failure. Targeting this process may be able to improve the outcome of cancer treatment. In the long run, however I notice, these approaches can only slow down tumor growth, but cannot eradicate cancer. My expectation to fight against cancers motivated me to find more powerful strategies that are promising to cure this disease. A close friend of mine who was working at Baylor Institute for Immunology Research (BIIR), Baylor Health Care System, Dallas, Texas, as a principal investigator, one day told me that BIIR was a world-leading institute for dendritic cell (DC)-based immunotherapy. He forwarded to me some of his research slides showing that intratumoral DC vaccination following chemotherapy causes complete disappearance of some tumors in his mouse models. I was so excited at viewing his research findings. It seemed to be promising as an effective cancer treatment.

The immune system has the greatest potential for the specific destruction of tumors with no toxicity to normal tissues. More importantly, the long-term immune memory can prevent cancer relapse. Considerable evidence by immuno-oncological research has indicated that tumors can be recognized by the immune system and their growth can be terminated or controlled by immunosurveillance. The emerging clinical data suggested that cancer immunotherapy is most likely to play a key role in the clinical management of cancers. Fortunately, I got a great opportunity to work at BIIR, as a Research Associate focusing on DC-based immunotherapy against cancers. BIIR, led by Dr. Banchereau, is among the top translational immunology research centers worldwide. Scientists at BIIR particularly concentrate their efforts on the studies of DCs, which are rare cells that turn on and regulate immune responses. Two-year experience of working at BIIR allowed me to study the functions of DC and to translate the research findings into novel approach to treat cancers in animal models.

More encouragingly, Dr. Steiman, Canadian immunologist at Rockefeller University, won the Nobel Prize for Physiology or Medicine in the year of 2011 for "his discovery of DCs and their role in adaptive immunity". He had been diagnosed as having pancreatic cancer and had received DC vaccination at BIIR. This therapy was proved to significantly prolong his life. But unfortunately, he passed away three days before the announcement of his winning the prize from the Nobel Committee.

After completing the 2-year fellowship, I joined the team led by Dr. Marc de Perrot in 2008, as a Research Associate, Latner Thoracic Surgery Laboratories, Toronto General Hospital, University Health Network, University of Toronto, Canada. Dr. de Perrot is the Head of Toronto Mesothelioma Research Program. The focus of our study is to improve the efficacy of mesothelioma treatment by immune modulation. Malignant pleural mesothelioma (MPM) is a rarely found cancer in the general population, but it is rather common among construction and industry workers who have been exposed to asbestos. MPM originates from the lining of the lungs (pleura), and is usually misdiagnosed until its advanced stage when treatment options are very limited and cure is no longer possible. As observed in other cancers, the immunosuppressive components are infiltrated into the tumor microenvironment of MPM patients. Therefore, we employed promising immunotherapy in combination with conventional therapies (i.e., surgery, radiotherapy, or chemotherapy) to treat mesothelioma. We have demonstrated that the number of regulatory T cells infiltrating into the MPM tumor increases over time after tumor challenge in mouse models, and depletion of this population can enhance anti-tumor immune reaction. Blockade of the immune suppressive signals, similarly as release of the brake, can induce specific immunity against tumor. These recent research findings, to my great honor, were presented at the 15th World Lung Cancer Conference held in October, 2013, Sydney, Australia. The abstracts of my two mini oral presentations can be viewed at MO20: Preclinical Therapeutic Models II, MO20.08 and MO20.09, respectively: http://www.2013worldlungcancer.org/documents/WCLC2013-AbstractBook.pdf.

I have worked in the field of cancer research for almost 30 years. On the way of scientific research to fight against cancers, countless scientists, like me, experienced hopes, successes and failures. No matter what the results of our present efforts are, I believe human would definitely win the fight against cancers.

I was very happy to talk with Ms. Grace Lee at the Exhibition Booth on the conference. She introduced about the new column "Between You and Me" in the *Journal of Thoracic Disease*. It was a great opportunity to share my story here with colleagues. I would like to thank you for your kind invitation.

Licun Wu, MD

Latner Thoracic Surgery Research Laboratories and Division of Thoracic Surgery, Toronto General Hospital, University Health Network, 101 College St., TMDT 2nd Floor, 2-818D, Toronto, ON, Canada

(Email: licunw@uhnres.utoronto.ca.)

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