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RECOLLECTION

Behind the Artemisinin, efforts and persistence from numerous scientists

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Professor Youyou Tu (China Academy of Chinese Medical Sciences, Beijing) was awarded the 2011 Lasker~DeBakey Clinical Medical Research Award for her contribution toward the discovery of Artemisinin, also known as Qinghaosu (Chinese: 青蒿素) and its utility for treating malaria (Zhang, 2011) in September 2011.

Malaria, a mosquito-borne parasitic disease, caused an estimated 225 million cases of infection and over 781,000 deaths in 2009 according to the 2010 World Health Organization (WHO) Malaria Report. Back in 1950s and 1960s, the treatment of malaria became more challenging due to drug resistance, demanding urgent need for new anti-malaria medicines. On May 23, 1967, the Chinese government launched a national project, Project 523, to fight against malaria. The project lasted over ten years and involved more than five hundred scientists of various disciplines from around sixty institutions throughout the country. Each of the scientists contributed to the discovery of Artemisinin in their own way, some isolating Artemisinin, some determining the molecular structure of Artemisinin, some synthesizing the derivatives of Artemisinin, while the others applying Artemisinin and its derivatives in clinical trials. It was one of the biggest team projects in China's S&T history ever, and Li Liang and Pengfei Li (deceased) were proud to be part of the team.

It was in 1975 when Li Liang and Pengfei Li were first contacted by Youyou Tu and her colleagues from the Institute of Chinese Materia Medica (ICMM). By then, Tu and her colleagues had isolated and crystallized Artemisinin, and had deduced the chemical composition and tried to elucidate its structure by Mass Spectrometry with aid from specialists of Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS). However, without knowledge on its molecular structure and absolute configuration, it was difficult to advance the functional study of Artemisinin. Therefore, ICMM asked for help from the Institute of Biophysics (IBP), CAS, an institute experienced in X-ray crystallographic determination of 3-dimensional Insulin structure. Two young scientists at IBP, Li Liang (Fig. 1) and Pengfei Li, took on the mission of determining the structure of Artemisinin.

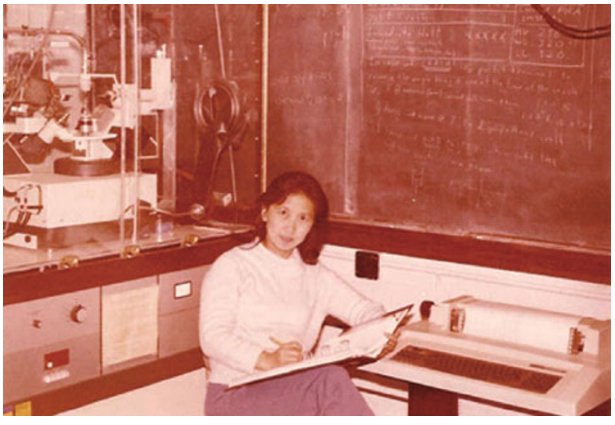

Figure 1. Dr. Li Liang in Dr. Philip Coppens' Lab when she was a visiting scholar at the State University of New York at Buffalo in 1981. A 4-circle X-ray Diffractometer is shown in the background.

A set of diffraction intensities of the Artemisinin crystal had been collected from a 4-circle X-ray Diffractometer at IBP. The next step would be solving the molecular structure with the diffraction intensities, and Li and Liang both thought of the Direct Methods, a mathematical approach from probability relationships to glean phase data from the diffraction intensities. It is a perfect approach for structural determination of small molecules like Artemisinin. This method was originally developed in the 1950s by Herbert A. Hauptman and Jerome Karle who were awarded the Nobel Prize for Chemistry in 1985 for their work.

By 1975, the Direct Methods had been applied in X-ray crystallography in the Western countries for over a decade, but had not yet been brought into China. With no prior

experience and little technical support, Liang and Li had to start from point zero, i.e., writing their own algorithms and computer programs based on the Direct Methods published in literature. Fortunate enough, they had access to the computers in the Beijing Computer Center despite of their busy schedule. Their computing times were routinely scheduled in the middle of the night. Every night, they would take the last bus to the Computer Center and then take the earliest bus back to IBP the next morning. Unlike the computers available nowadays, they had to use the punched paper tapes to feed their programs into the computer TQ-16, an early Chinese Minicomputer Mode. The workload was unimaginable to those of us who are accustomed to computer technology in the 21st century. With the heavy workload and his pre-existing kidney disease, Li finally succumbed to overfatigue and was hospitalized in the early spring of 1976. Liang continued working on debugging the programs. After another long night at the Computer Center, Liang finally finished debugging the Direct Methods program. The next morning, she rushed over to tell Li the good news, but was told that Li had just passed away hours before. It was regrettable that Li did not get to see the Artemisinin molecular model determined with his and Liang's programs. This was the very first crystal structure determined by the Direct Methods in China.

The R-factor (a measure of the agreement between the structural model and the experimental X-ray diffraction intensities in crystallography) of Artemisinin structure at the time was around 20%, far from the acceptable international standard for small molecule structures. Thus Liang introduced and applied the advanced Least-Square approach to refine the structural model by her programs. She was so immerged in her work that even her toddler son knew the term "Least-Square" because "Mommy mumbled it in her sleep." Finally, in 1977, she completed the structural determination of Artemisinin (Fig. 2) with the R-factor down to 5% (Qinghaosu Coordinating Research Group at the Institute of Biophysics, 1979), which was the first crystal structure with such a low R-factor in China. The established crystal structure and chemical absolute configuration, which laid foundation for the recognition of Artemisinin by the WHO, won the National Technology Invention Award (second place) in 1979.

As mentioned at the beginning of this article, Liang and Li and their work were only a small part of Project 523, which included more than five hundred scientists with their diligent contribution. That partly explained why such an important discovery could be made during the difficult time of "Cultural Revolution" in China. Another reason was the full support by the government. The Project 523 Office was under direct

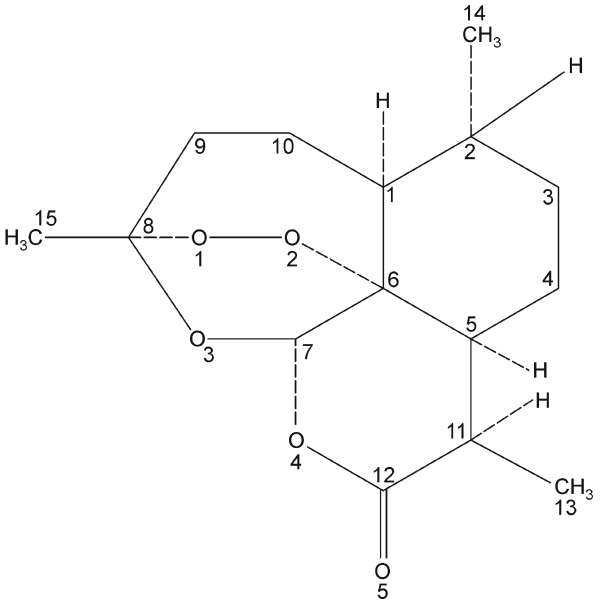

Figure 2. Molecular structure of Artemisinin (Qinghaosu Coordinating Research Group at the Institute of Biophysics, 1979).

supervision of the late Prime Minister Enlai Zhou; and even though China was short of every kind of resources in 1960s and 1970s, the research institutes were provided with sufficient funding to purchase advanced equipments such as the 4-circle X-ray Diffractometer at IBP. Back to the present, China's R&D investment over the past decade has been tremendously increased, and China now has more scientific researchers than ever before. Taking all of these into account, we can expect more and more critical scientific breakthroughs in China in the near future.

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