

The discovery of artemisinin and the Nobel Prize in Physiology or Medicine

SU Xin-Zhuan* & MILLER Louis H.*

Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases,
National Institutes of Health, Bethesda, MD20892, USA

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1 Summary

The 2015 Nobel Prize in Physiology or Medicine was awarded to Professor Tu Youyou for her key contributions to the discovery of artemisinin. Artemisinin has saved millions of lives and represents one of the significant contributions of China to global health. Many scientists were involved in the previously unknown 523 Project, and the Nobel Prize given to a single person has not been without controversy. Here we summarize some key events in the 523 Project and present our views on the Award to help the public better understand the rationale of the Nobel Committee's decision, the significance of the discovery, and current issues related to artemisinin in treating malaria.

2 Introduction

The discovery of artemisinin dramatically changes the landscape to combat malaria and leads to a paradigm shift in antimalarial drug development. According to a recent WHO report, 97 countries have ongoing malaria transmission, and an estimated 3.4 billion people are at risk of malaria, of whom ~1.2 billion are at high risk (http://www.who.int/malaria/publications/world_malaria_report_2014/en/). The good news is that between 2000 and 2012, the malaria incidence rates were reduced by 25% globally, and the

global malaria mortality rate was reduced by 42% during the same period. Many countries are now on track for declaring malaria-free status. Artemisinin and its derivatives have played a key role in malaria related mortality. According to a recent estimate, approximately 22% of the 663 million averted clinical cases were due to the use of artemisinin combination therapies (ACTs) [1].

Artemisinin represents a new class of antimalarial drugs, which leads to two paradigm shifts in antimalarial research and therapy. The first one is the change from quinine-based antimalarial drugs to artemisinin-based therapies due to the emergence of parasites resistant to quinoline drugs. Currently, ACTs are the drugs recommended by WHO for treating the deadly *Plasmodium falciparum* infections and are being used worldwide (<http://www.who.int/malaria/publications/atoz/9789241549127/en/>).

The second paradigm shift is the change of research direction in antimalarial drug development. Artemisinin and its derivatives are in a new class of antimalarial agents with unique structure (1,2,4-trioxane peroxide pharmacophore), which has become a new direction for antimalarial drug development. For example, some of the most promising drugs under clinical trials, including OZ277 and OZ439, are synthetic peroxides with key structures similar to artemisinin [2,3]. Additionally, research related to artemisinin has been a hot topic in malaria and other fields such as antiviral and anticancer treatments in the past 15 years [4]. A search of PubMed for key word 'artemisinin' identified 2,869 articles published in the last three years. The discovery of ar-

*Corresponding author (email: xsu@niaid.nih.gov; lmill@niaid.nih.gov)

artemisinin changes the direction on how we treat malaria and how we develop and search for new antimalarial drugs. The impacts on global health and the paradigm shifts in antimalarial drug research are the key factors that the Nobel Committee considered when they evaluated all the nominations.

3 A brief history of artemisinin discovery

Artemisinin was discovered during the Chinese “Cultural Revolution” in the 1970s, at a time when scientific research was not allowed, and results from ongoing projects such as the 523 Project were not published. In response to a request from the Vietnam government for help on malaria treatment, the Chinese government launched a secret operation called 523 Project. On May 23 (523), 1967, a meeting was held in the Beijing to discuss plans for the search, which officially launched the project. Professor Tu was brought into the project in January, 1969 when Mr. Bai BingQiu and Mr. Zhang JianFang (523 Project directors) visited the Institute of Chinese Materia Medica (ICMM) and asked for help. Professor Tu became involved in the 523 Project after the visit and was designated as a team leader to search for Chinese herb recipes having antimalarial activities.

Professor Tu’s group started with a search for recipes that had been used to treat fever. They searched more than 2,000 recipes and compiled 640 recipes for further evaluation within three months. They then looked at the individual plant names that had high frequencies of appearance in the recipes. A plant called ‘Qinghao’ or *Artemisia annua* was one of the plants that appeared in the recipes frequently. Professor Tu’s group tested extracts from more than 100 plants on rodent malaria parasite *Plasmodium berghei*. An extract from *A. annua* had ~68% inhibition rate initially, but the activity was not stable, varying from 12%–40% inhibition in subsequent repeats. The variation in antimalarial activity could be due to many factors, including (as reported by Professor Tu in the 1972 presentation to the scientists in the Project) geographic origins of the plant, seasonal variation, different parts of the plant (leaves or stem) and the methods used in extraction. One day, Professor Tu was reading some recipes written by Ge Hong ~1700 years ago. In one of his recipes, Ge Hong described how to obtain ‘juice’ from Qinghao (*A. annua*) plant to treat fever using cold water, instead of the traditional methods of boiling herbs for preparing Chinese medicines. Professor Tu suddenly realized that high temperature could be the cause of instability in antimalarial activity they experienced. The second hint Professor Tu had from Ge Hong’s description was that the plant leaf was likely the part having the most activity because the ‘juice’ could be obtained from the leaves much easier than other parts of the plant. She decided to use ether, replacing ethanol, to extract the active ingredients from the plant leaves and obtained sample #191 that could inhibit rodent malaria (October, 1971) and monkey

malaria with 100% activity in December, 1971. Professor Tu presented her work at a meeting held in Nanjing on March 8, 1972. Her results were exciting, and the leadership of the 523 Project decided that she should conduct a clinical trial in the same year. In August 1972, Professor Tu led a clinical trial team to Hainan Island and tested her extracts on 21 patients, achieving 95%–100% efficacy after taking the medicine herself to evaluate the safety of the extract. Professor Tu reported the results from the clinical trials in a meeting held in November 17, 1972. The exciting results led to a large-scale, countrywide effort to extract large quantities of the pure ingredient (or artemisinin crystal) to determine its structure and to chemically synthesize artemisinin involving a large number of scientists from many institutions. These key events are supported by documents or presentations of the 523 Project provided by Professor Tu.

4 Professor Tu’s major contributions in the discovery of artemisinin

4.1 Professor Tu played a critical role in the discovery of artemisinin. Her major contributions are:

(1) Bringing the plant into the 523 Project. Hundreds of scientists were involved in the 523 Project; however, Professor Tu was the person who brought *A. annua* into the 523 Project or re-discovered the plant. In a 523 meeting summary dated June 1, 1971, the scientists of the 523 Project discussed progress, including the identification of different herbs/plants with antimalarial activities, but did not mention the *A. annua* plant (Figure 1A), suggesting that they were NOT aware of the antimalarial activity of the *A. annua* plant at that time (or it was not among their priorities). Nine months later on March 8, 1972, Professor Tu described her discovery of extract from *A. annua* and showed that the extract was effective in treating *P. berghei* at another 523 meeting held in Nanjing (Figure 1B). These two classified 523 Project documents clearly showed that Professor Tu was the person who brought *A. annua* into the 523 Project.

(2) Professor Tu discovered a method to extract active ingredient. In her presentation dated March 8, 1972, Professor Tu described a procedure for extracting stable and active antimalarial extract (neutral portion). They replaced ethanol (boiling point 78°C) with ether (boiling point 35°C) in the extraction, which greatly improved the stability of the active ingredient. Other groups in the 523 Project were able to obtain high quality of artemisinin crystals after hearing her report. There were two letters sent to Tu’s institute (Yunnan Institute of Pharmacy and Shangdong Institutes of Parasitology, respectively) in 1973 that expressed gratitude for sharing information on artemisinin extraction. A copy of each letter can be found in the book titled “Qinghao and Qinghaosu Derivative Drugs” (page 40) [5]. Therefore,

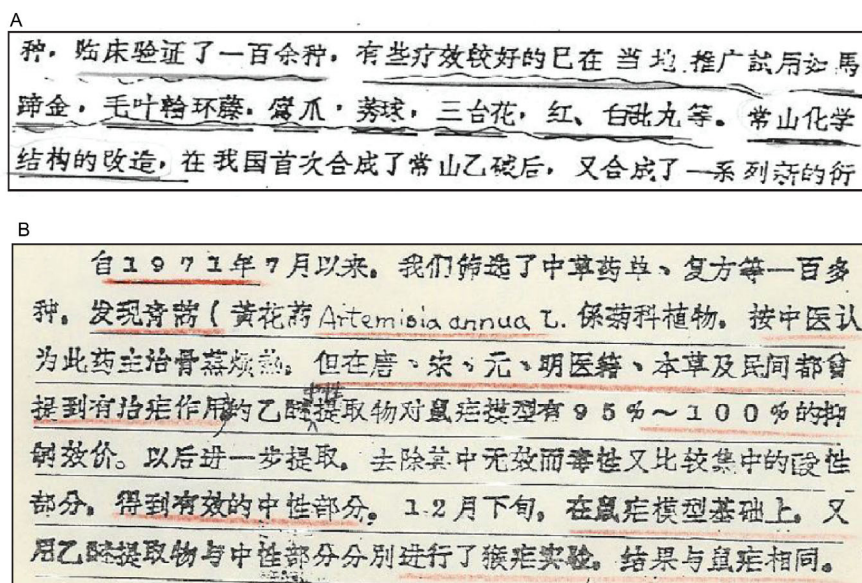


Figure 1 Images of partial 523 Project meeting summary and Professor Tu's 1972 presentation. A, The meeting summary of June 1, 1971 listed seven Chinese herbs that were the focuses at that time, but no mention of Qinghao plant. B, A paragraph of Professor Tu's 1972 (March 8) presentation describing results of 95%–100% efficacy from rodent and monkey experiments using the neutral portion of her ether extract (with permission from the document provider).

Professor Tu was the person who discovered an efficient method for extracting the active ingredient from the *A. annua* plant.

(3) Professor Tu conducted the first clinical trial of *Artemisia* extract in human patients. Professor Tu also led a team to Hainan and conducted the first clinical trial in humans in August 1972. They tested the drug in 11 cases of *Plasmodium vivax*, 9 cases of *Plasmodium falciparum*, and 1 case of a mixed infection. All the patients quickly returned to normal temperature from 40°C, and many were negative of parasites in the blood smear. The results were better than those of the control group given chloroquine. Later, they tested another 9 cases in Beijing and obtained similar results. She wrote a report and presented the results in a 523 Project meeting held on November 17, 1972 [5], setting off a large-scale effort to isolate the active ingredient. This also was the time when other scientists received instructions to work on artemisinin related projects. Thus, Professor Tu was the person who conducted the first successful clinical trial in human.

(4) Isolation of active ingredient for structural studies. Following the demonstration of antimalarial activity, her group continued to isolate the active ingredient. They obtained a white crystal that had melting point of 156–157°C with molecular weight of 282 in November 8, 1972, which they named Qinghaosu. They showed that 50–100 mg kg⁻¹ dosages could cure rodent malaria parasites. The isolation of the crystal allowed further investigation of its chemical structure. She coordinated with scientists in Beijing and Shanghai and played a role in determining the structure us-

ing the crystal they obtained.

(5) The discovery of dihydroartemisinin. Professor Tu also discovered dihydroartemisinin that greatly improved water solubility.

Because of her many critical contributions, the Chinese Ministry of Health issued a 'New Drug Certificate for Artemisinin' to her institute in 1986 [5], suggesting official recognition of her discovery. Her institute also received certificate of new drug for dihydroartemisinin.

4.2 National and international recognition of her contributions in the discovery of artemisinin and derivatives.

Because of her critical contributions and achievements in the discovery, Professor Tu received numerous awards from the Chinese government and private organizations worldwide, including the National Scientific Discovery Award for the Antimalarial Drug—Qinghaosu by the Ministry of Science and Technology in 1979; the National Model Worker by the State Council in 1995; the Outstanding Scientific Achievement Award by Qiu Shi Science and Technologies Foundation of Hong Kong in 1996; Achievement Award in New China by the Ministry of Health in 1997; Prince Mahidol Award, Prince Mahidol Award Foundation, Thailand in 2003; Award for Development of Chinese Materia Medica, Cyrus Chung Ying Tang Foundation in 2009; the Albert Lasker Award for Clinical Medical Research in 2011; GlaxoSmithKline Outstanding Achievement Award in Life Sciences in 2011; The Warren Albert Foundation

Prize in 2015; the 2015 Nobel Prize in Physiology or Medicine.

4.3 Other evidence supporting Professor Tu's key role in the discovery

As mentioned above, Professor Tu was one of the 10 people who received an award from the Qiu Shi Science and Technologies Foundation of Hong Kong for contributions to the 523 Project in 1996. She was described as "the inventor of new antimalarial drugs artemisinin and dihydroartemisinin".

Professor Li GuoQiao (a participant of the 523 Project and one of the 10 Qiu Shi Awardees) confirmed that Tu was the first person who discovered artemisinin in his interview with news media after the Lasker Award presented to Professor Tu in 2011 (http://gzdaily.dayoo.com/html/2011-09/29/content_1489532.htm).

The following is a question to Professor Li GuoQiao during an interview after Tu's Lasker Award: "If you were awarded with the Lasker Award, who else should receive the Award too?" Professor Li said he filled in Tu YouYou first, Mrs Luo ZheYuan, the second. Similarly, another Qiu Shi Awardee Mr. Liang JuZhong said: "First of all, I want to congratulate Tu YouYou for winning the Award. As the discoverer of artemisinin, she deserved the honor" during an interview with reporter.

Professor Zhou WeiShan (a chemist who played a key role in structure determination and synthesis of artemisinin and also one of the Qiu Shi Awardees), interviewed by Chinese reporters some years ago, also credited the key contribution to Professor Tu (<http://emuch.net/html/200903/1242552.html>).

The following are quotations and answers during Professor Zhou WeiShan's interview with Chinese "Science Times" in December 2009. The original article was in Chinese. We include a brief translation: Tu YouYou joined the 523 Project as a team leader in January 1969. The other scientists screened over 40,000 herbs and compounds, but no satisfactory results. Tu YouYou decided to search traditional Chinese medicinal books and interview Chinese traditional medicine doctors. She compiled more than 640 recipes, many of them contained Qinghao. The initial results were not satisfactory, and she read more traditional medicinal books. Some sentences from Ge Hong's writing attracted her attention 'A bunch of Qinghao, squeeze in two liters of cold water, and drink the juice'. This description was different from the traditional methods of boiling Chinese herbs. She decided to use ether at 60°C boiling point (as cited in the interview) for extraction. She observed 100% inhibition on October 4, 1971. On March 1972, Tu YouYou reported her results at a 523 meeting held in Nanjing. In 1973, the activity of artemisinin crystal was verified in

Yunnan region. The 523 Office decided to name the crystal Qinghaosu and to develop it as a new drug. In 1973, the Institute of Chinese Materia Medica obtained Qinghao crystal and was looking for chemists who could help determine the structure. Mr. Zhou was not the first person they contacted. Mr Zhou's description matches the history described above.

5 The emergence of artemisinin tolerant parasites

Due to the large-scale use of artemisinin in recent years, *P. falciparum* parasites that are potentially resistant (or more tolerant) to the drug have been reported in countries in Southeast Asia [6,7]. Although the classical drug resistant parasites that can survive constant drug pressure have not been found, parasites that can survive longer in patients after standard ACT treatments are reducing parasite cure rate and patient recovery. Artemisinin has a short half-life *in vivo*, and it is used for treating malaria infections, not for prophylaxis. Professor Tu has been trying to raise public awareness of this serious issue for years.

6 Credits and controversies

There have been many controversial issues associated with credits and contributions to the 523 Project and the discovery of artemisinin. It is a fact that a large number of people took part in and contributed to the project, including leadership from the People's Liberation Army. All later work was based on her initial demonstration of active ingredient from the Qinghao plant. We can only imagine what the future would have held if Professor Tu had not presented her results at the March 8 (1972) 523 meeting in Nanjing. The project might have focused on other leads instead of the Qinghao plant. In this sense, the project actually greatly benefited from her discovery. Without her initial presentation on March 8, 1972, there would have been no other Qinghao crystals obtained by other institutes, no work on chemical structure, no artemisinin derivatives synthesized, and no clinical trials. Often when multiple people are involved in an important research development, The Nobel Prize Committee recognizes only the individual who made the seminal discovery that led to the development. For example, the Nobel Prize went to Harald Zur Hausen for the discovery of the papillomavirus in cervical cancer and not to others who later developed the vaccine.

7 Conclusions

There is no doubt that Professor Tu is the first person who

brought the *A. annua* into the 523 Project, the first person who obtained the active ingredient (extract and crystal), and the first person who demonstrated antimalarial activity in humans. The impact of artemisinin on public health is immediate and tremendous. Millions of lives have been saved by the use of artemisinin. Additionally, the discovery of artemisinin has led to paradigm shifts in antimalarial research and therapy. There are few scientific discoveries that have the same scale and instant impacts on public health, human productivity, and scientific research as artemisinin has!

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