HHS Public Access

Author manuscript

Sci China Life Sci. Author manuscript; available in PMC 2016 July 29.

Published in final edited form as:

Sci China Life Sci. 2015 November ; 58(11): 1175–1179. doi:10.1007/s11427-015-4948-7.

The discovery of artemisinin and Nobel Prize in Physiology or Medicine

Xin-zhuan Su and **Louis H. Miller**

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

Xin-zhuan Su: xsu@niaid.nih.gov; Louis H. Miller: lmiller@niaid.nih.gov

Summary

The 2015 Nobel Prize in Physiology or Medicine was awarded to Professor Youyou Tu 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 summarized 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 artimisinin in treating malaria.

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 [1]. 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) [2].

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 quinoline-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 [3]. 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 [4, 5]. Additionally, research related to artemisinin has been a hot

topic in malaria and other fields such as antiviral and anticancer treatment in the past 15 years [6]. A search of PubMed for key world ‘artemisinin’ identified 2869 articles published in the last three years. The discovery of artimisinin changes the directions 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.

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 publically. 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 Beijing Hotel to discuss plans for the search, which officially launched the project. Professor Tu was brought into the project in January, 1969 when the 523 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 designed 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 2000 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 *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 Prof Tu in 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 and monkey malaria with 100% activity on October 4, 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% inhibition 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 on November 17, 1972. The exciting results led to a large-

scale, countrywide effort to extract large quantities of the pure ingredient (or arteimisinin crystal) determine its chemical structure and synthesis 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.

Professor Tu's major contributions in the discovery of artemisinin

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's 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 (Fig. 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 Project meeting held in Nanjing (Fig. 1b). These two classified 523 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 (35°C boiling point) 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 (Yunan Institute of Pharmacy and Shangdong Institutes of Parasitology) 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" 《青蒿及青蒿素药物》(page 40)[7]. Therefore, Porfessor Tu's 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 temperate from 40°C, and many were negative of parasites in the blood smear. The results were better than 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 meeting held on November 17, 1972 [7], setting off a large-scale effort to isolate the active ingredient. Thus, Professor Tu was the person who conducted the first successful clinical trial in human using Artemisia extract.

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

5. . **The discovery of dihydroartemisinin**. Professor Tu also discovered dihydroartemisinin that greatly improved water solubility and treatment efficacy.

Because of her many critical contributions, the Chinese Ministry of Health issued a ‘New Drug Certificate for Arteminisin’ to her institute in 1986 [7], suggesting official recognition of her discovery. Her institute also received certificate of new drug for dihydroartemisinin and many other treatment pills.

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, including National Scientific Discovery Award for Antimalaria Drug-Qinghaosu by the Ministry of Science and Technology in 1979; National Model Worker by the State Council in 1995; Outstanding Scientific Achievement Award by Qiu Shi Science and Technologies Foundation of Hong Kong in 1996; Achievements in New China by Ministry of Health in 1997; Prince Mahidol Award, Prince Mahidol Award Foundation, Tailand in 2003; Award for Development of Chinese Materia Medica, Cyrus Chung Ying Tang Foundation in 2009; Albert Lasker Award for Clinical Medical Research in 2011; GlaxoSmithKline Outstanding Achievement Award in Life Science in 2011; The Warren Albert Foundation Prize in 2015; the 2015 Nobel Prize in Physiology or Medicine in 2015, and more.

Other evidence supporting Professor Tu’s key role in the discovery

Professor Li Gouqiao (李国桥, a participant of the 325 project) 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 Guoqia during an interview after Tu’s Lasker Award: “如果你获得了这个奖，你认为还有谁应该获奖？”李国桥当时填了两个人，第一个是屠呦呦，第二个是罗泽渊. (Translation:

There was a question in the Lasker form he had to fill: “If you were awarded with Lasker Award, who else should receive the Award too?” Professor Li said he filled in Tu Youyou first, Mrs Lou Zheyuan the second).

Professor Zhou Weishan (周维善, a chemist who played a key role in structure determination and synthesis of artemisinin), 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 Report/Time” in March 2009. The original article was in Chinese. We include a brief translation:

1969 年 1 月，屠呦呦以中医研究院科研组长的身份，参加了“五二三项目”。(Youyou Tu joined the 523 Project as a team leader in January 1969). 此前，国内其他科研人员已经筛选了 4 万多种抗疟疾的化合物和中草药，没有令人满意的结果。(The other scientists screened over 40,000 herbs and compounds, but no satisfactory results). 屠呦呦决定从系统整理历代医籍开始，也四处走访老中医，她整理了一个 640 多种包括青蒿在内的草药《抗疟单验方集》。(Tu decided to search traditional Chinese medicinal books and interview Chinese traditional medicine doctors. She organized more than 640 recipes, many of them contain Qinghao). (The initial results were not satisfactory, and she read more traditional medicinal books. Some sentences from Mr. Ge Hong’s writing attracted her attention ‘A bunch of Qinghao, squeeze in two liters of cold water, and drink the juice’. This description is different from the traditional methods of boiling Chinese Herbs. She decided to use ether at a 35°C (Note: 60°C by Mr Zhou) boiling point for extraction. She observed 100% inhibition on October 4, 1971). 1972 年 3 月，屠呦呦在南京召开的“五二三项目”工作会议上报告了实验结果；1973 年，青蒿结晶的抗疟功效在云南地区得到证实，“五二三项目”办公室于是决定：将青蒿结晶物命名为青蒿素，作为新药进行研发。(On March 1972, Youyou Yu reported her results at a 523 meeting held in Nanjing. In 1973, the activity of artemisinin crystal was verified in Yunan region. The 523 Office decided to name the crystal Qinghaosu and to develop it as a new drug). 1973 年初，北京中药研究所拿到青蒿素的结晶，寻找能够解开其结构的有机化学家，但最初找到的人并不是周维善。(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.

The emergence of artemisinin tolerant parasites

Due to large-scale use of artemisinin in recent years, parasites that potentially resistant (or more tolerance) to the drug have been reported in countries in Southeast Asia [8, 9]. Although the classical drug resistant parasites that can survive constant drug pressure *in vitro* 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.

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 and contributed to the project, including the leadership from the people's liberation army. But please remember, all other 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 Qinghau plant. In this sense, the project actually greatly benefited from her discovery. Without her initial presentation on March 8, 1972, there would have had no Qinghao crystals obtained by other institutes, no work on chemical structure, no artemisinin derivatives synthesized, and no related 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.

Conclusions

There is no doubt that Professor Tu (her group) 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 human. 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!

Acknowledgments

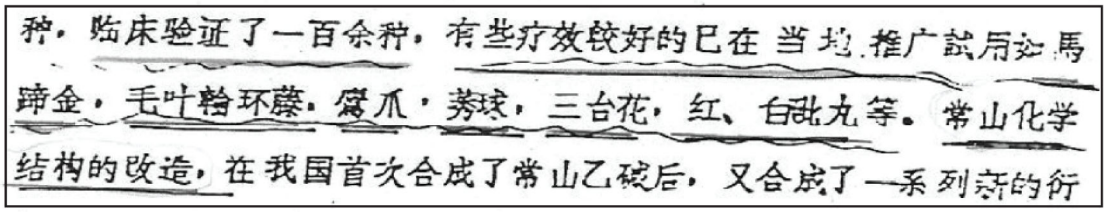
This work was supported by the Division of Intramural Research at the National Institute of Allergy and Infectious Diseases (NIAID).

References

1. WHO. World malaria report 2014. 2014. http://wwwwhoint/malaria/publications/world_malaria_report_2014/en/
2. Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on *Plasmodium falciparum* in africa between 2000 and 2015. Nature. 2015; 526:207–211. [PubMed: 26375008]
3. WHO. Guidelines for the treatment of malaria third edition - 2015. 2015. http://wwwwhoint/malaria/publications/atoz/9789241549127/en/
4. Charman SA, Arbe-Barnes S, Bathurst IC, et al. Synthetic ozonide drug candidate oz439 offers new hope for a single-dose cure of uncomplicated malaria. Proc Natl Acad Sci U S A. 2011; 108:4400–4405. [PubMed: 21300861]
5. Reiter C, Frohlich T, Zeino M, et al. New efficient artemisinin derived agents against human leukemia cells, human cytomegalovirus and *Plasmodium falciparum*: 2nd generation 1,2,4-trioxane-ferrocene hybrids. Eur J Med Chem. 2015; 97:164–172. [PubMed: 25965779]
6. Ho WE, Peh HY, Chan TK, et al. Artemisinins: Pharmacological actions beyond anti-malarial. Pharmacol Ther. 2014; 142:126–139. [PubMed: 24316259]
7. Tu, Y.; Wang, J.; Wang, M., et al. Qinghao and qinghaosu derivative drugs. Beijing: Chemical Industry Publication; 2009.
8. Ashley EA, Dhorda M, Fairhurst RM, et al. Spread of artemisinin resistance in plasmodium falciparum malaria. N Engl J Med. 2014; 371:411–423. [PubMed: 25075834]

9. Dondorp AM, Nosten F, Yi P, et al. Artemisinin resistance in plasmodium falciparum malaria. N Engl J Med. 2009; 361:455–467. [PubMed: 19641202]

A


种，临床验证了一百余种，有些疗效较好的已在当地推广试用如马
蹄金，毛叶轮环藤，穿瓜，莠球，三台花，红、白蛇九等。常山化学
结构的改造，在我国首次合成了常山乙碱后，又合成了一系列新的衍

B

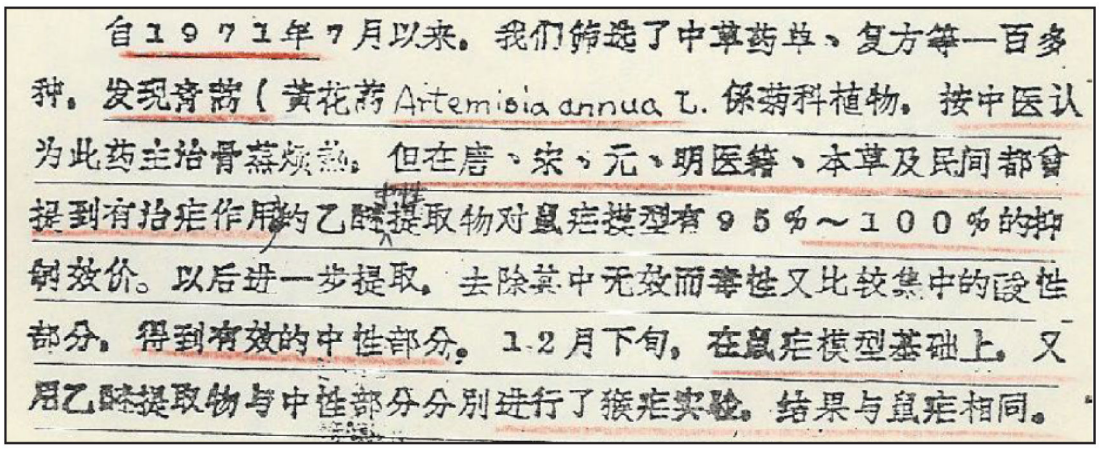

自1971年7月以来，我们筛选了中草药单、复方等一百多
种，发现青蒿（黄花蒿 Artemisia annua L. 保菊科植物，按中医认
为此药主治骨蒸烦热，但在唐、宋、元、明医籍、本草及民间都曾
提到有治疟作用的乙醚提取物对鼠疟模型有95%～100%的抑
制效价。以后进一步提取，去除其中无效而毒性又比较集中的酸性
部分，得到有效的中性部分。1.2月下旬，在鼠疟模型基础上，又
用乙醚提取物与中性部分分别进行了猴疟实验，结果与鼠疟相同。

Figure 1.

Images of partial 523 Project meeting summary (A) and Professor Tu's 1972 presentation (B). **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 95–100% efficacy from rodent and monkey experiments using the neutral portion of her ether extract.