From Artemisinin to Antimalarial Drugs: A Role Model of Scientific Collaboration

—— An Interview with Academician CHEN Kaixian on China's First Nobel Prize in Sciences

On December 10, pharmocologist TU Youyou from the China Academy of Traditional Chinese Medicine was awarded the 2015 Nobel Prize in Physiology or Medicine in Stockholm, "for her discoveries concerning a novel therapy against Malaria". As the first Chinese citizen to receive a Nobel Prize in sciences, she has been under the spotlight and her stories celebrated by many. *BCAS* reporter XIN Ling had the privilege to talk to Dr. CHEN Kaixian, TU's peer and a distinguished medicinal chemist, who is former director of the CAS Shanghai Institute of Materia Medica and current president of Shanghai Science and Technology Association. He talked about how the artemisinin-based antimalarial drugs were developed in China during the 1960s and 70s, and how this success as a role model of scientific collaboration could shed light on the country's research efficiency and innovation dilemma.

BCAS: How was artemisinin discovered and developed into a "wonder drug" against malaria that has saved millions of lives across the world?

CHEN: Back in the 1950s, malaria was mainly treated with quinine, which was separated from the cinchona trees in South America, with declining success due to growing drug resistance. During the Vietnam War, due to the hot and humid local environment, many Chinese soldiers were plagued by the deadly disease. The non-combatant injury and death toll became so high in the end that the Chinese leadership made an appeal to the scientific community, for scientists to come together and look for a new anti-malarial drug. On May 23, 1967, a special administrative unit called "Office 523" was set up to coordinate the work of more than 500 researchers from over 60 research institutions involved in this study. The office effectively bridged interdisciplinary and institutional gaps, and optimized the allocation of limited research resources. There were only two such nation-level medical collaboration efforts at that time, the other being chronic bronchitis study. The R&D of antimalarial drugs turned out to be a huge success.

Under the coordination of Office 523, the hunt went on across the country for all possible ways that might lead to a therapy to eradicate malaria. For instance, a group at the Shanghai Institute of Materia Medica (SIMM) under CAS investigated a traditional herb known as the Chinese Quinine (*Dichroa*

TU Youyou

TU Youyou (left) as a kid and her mother.

Tu Youyou is a medical scientist and pharmaceutical chemist who became the first Chinese Nobel laureate in physiology or medicine and the first citizen of the People's Republic of China to receive the Nobel Prize in natural sciences in October 2015.

"Youyou Tu searched ancient literature on herbal medicine in her quest to develop novel malaria therapies. The plant *Artemisia annua* turned out to be an interesting candidate, and Tu developed a purification procedure, which rendered the active agent, Artemisinin, a drug that is remarkably effective against Malaria," stated the Nobel Assembly at Karolinska Institutet in its official press release.

Born in the port city of Ningbo, Zhejiang Province in 1930, TU was named after a verse in the *Book of Songs*, a collection of ancient Chinese poetry that is believed to have been compiled by Confucius. In 1951, she enrolled at the Peking University School of Medicine and graduated four years later from its Department of Pharmacology. After graduation, she started working at the Academy of Traditional Chinese Medicine. In 1969, she was recruited to a confidential medical research project, dubbed "Project 523" under the instruction of the Chinese central government, to find a drug that would cure malaria. She was appointed head of the project at her Academy.

In the rainforests of southern China, Tu witnessed the mosquito-borne disease's devastating toll on the human body. Back in Beijing, she and her coworkers started scouring books about traditional Chinese medicine for leads on substances that might help them defeat malaria, and they finally identified an active compound in a plant called sweet wormwood (Artemisia annua), with inspiration from a hundreds-of-years-old book *The Manual of Clinical Practice and Emergency Remedies*. In 1972, her team obtained the pure substance and named it qinghaosu, or artemisinin, and TU took it upon herself to test it. The treatment worked and was proved safe for humans. Since then, artemisinin-based antimalarial drugs have saved millions of lives, especially in the developing world.

TU shared the Nobel Prize in Physiology or Medicine 2015 with William C. Campbell and Satoshi Ōmura. She is also winner of a number of other international awards including the prestigious Lasker DeBakey clinical medical research award in 2011.

She is jokingly regarded as a "Professor of Three Noes" – no postgraduate degree, no study or research experience abroad, and not a member of any Chinese national academies. She is married to Li Tingzhao, a metallurgical engineer and her former middle school classmate. They live in Beijing and have two daughters. (Agencies)

Back in the 1950s, TU Youyou, then as a research intern, was studying herbs with her teacher LOU Zhiceng at the Institute of Chinese Materia Medica in Beijing.

febrifuga), which was used for malaria treatment in ancient China. Their experiments confirmed the herb's antimalarial efficacy, but also revealed its severe side effects on the cardiovascular system. They had to give it up.

Around the same time, pharmacologist TU Youyou and her group at the China Academy of Chinese Medical Sciences were also experimenting extensively on the subject. One of her interests was a plant called sweet wormwood (*Artemisia annua*). From *Handbook of Prescription for Emergency Remedies*, which is a classic of traditional Chinese medicine (TCM) written by alchemist GE Hong in the Eastern Jin Dynasty, TU came to know that sweet wormwood could serve as a cure for malaria. The main idea was to soak a handful of the plant with two liters of water, extract the juice by twisting, and then drink it all. She decided to follow up this clue.

Like many other teams, their research went through ups and downs, and TU's pioneering role was mainly established in three aspects. First and foremost, she was the first person to bring the "sweet wormwood idea" to Project 523. For the first time, she proposed and implemented a systematic study on the plant for malaria treatment. Secondly, she was the first to come up with the correct method to isolate from *Artemisia annua* its active ingredient — artemisinin, with 100% antimalarial activity. In the beginning, her group was following the routine extraction methods for natural products which involve repeated heating, distillation, condensation using water or ethanol. However, the results fell short of everyone's expectation: the bioactivity observed was not strong in the extracts. After 190 failures, TU revisited GE Hong's book. This time she noticed that the author did not mention anything about heating. The water he described was probably just of room temperature. It inspired her to immediately try another common extraction agent, diethyl ether, which works under normal temperature without any heating processes. And this new isolation method turned out to be a great success. TU's third contribution was to confirm for the first time that the clinical efficacy of artemisinin could reach 100%, after a series of tests in mice carried out by her group.

Their findings were soon spread within Project 523 and inspired a wide range of artemisinin-related studies. However, the first artemisinin-based antimalarial drug was plagued by two major drawbacks. One was its poor solubility in both water and oil leading to the only possible drug form of suppository, which means progressive dissolution and absorption incapable of emergency treatment in critical conditions. The other was its relatively

high recurrence rate. So artemisinin was promising but further studies were needed.

To address these drawbacks, Office 523 assigned the CAS Shanghai Institute of Organic Chemistry (SIOC) with a new mission: to determine artemisinin's structure. TU handed over her samples to a group of researchers at SIOC, who was led by organic chemist ZHOU Weishan. With concerted efforts from the CAS Institute of Biophysics, ZHOU's team successfully cracked the artemisinin structural myth: it contains a seven-membered ring, featuring a very unusual peroxide bridge in the center.

With such a structural analysis result in hand, the next step was to synthesize new compounds. Through structural modification with artemisinin as the lead compound, researchers from SIMM synthesized nearly a hundred kinds of derivatives. Among them, artemether developed by LI Ying's group demonstrated the best bioactivity and stood out as the most promising candidate for a new generation of antimalarial drugs. It had excellent oil solubility, and patients treated with artemether suffered from much lower recurrence rate. Also, experts from Guilin Pharmaceutical Company developed another competitive candidate called the artesunat, which can be taken orally or via injection.

Compared with the suppository, artemether and artesunat remarkably improved the efficacy and usefulness of the drug. They have been widely applied in malaria-ridden regions across the world since then.

The artemisinin suppository was approved as a new drug by China's drug administration in 1986. A year later, Artemether and Artesunat received their drug approvals. Then in 1992, Dihydroartemisinin developed by TU's group came to join the artemisinin drug family. In the United States, scientists went on to synthesize arteether and similar types of drugs based on artemisinin.

We all know that African countries were extremely affected by malaria. The annual infection and death cases could hit as much as 200 million and 600,000 people, respectively. Thanks to artemisinin, up to five million lives have been spared from the death threat of malaria so far. In some villages in the Comoros, which is an island nation off Africa's east coast, about 90% of people used to carry the disease. Now with artemisinin drugs, malaria has been basically wiped off the island.

BCAS: What are the other significances concerning the discovery of artemisinin, from a scientist's perspective?

CHEN: I think its unique chemical structure is of

Malaria

A malaria clinic near the Thai-Burma border. Artemisinin has been Thailand's most potent weapon in the long-running battle against malaria, contributing to a sharp drop in deaths. Photograph: Pornchai Kittiwongsakul/AFP/Getty Images

Key facts

• Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected female mosquitoes.
• About 3.2 billion people – almost half of the world's population – are at risk of malaria.
• Young children, pregnant women and non-immune travelers from malaria-free areas are particularly vulnerable to the disease when they become infected.
• Malaria is preventable and curable, and increased efforts are dramatically reducing the malaria burden in many places.
• Between 2000 and 2015, malaria incidence (the rate of new cases) fell by 37% globally. In that same period, malaria death rates fell by 60% globally among all age groups, and by 65% among children under 5.
• Sub-Saharan Africa carries a disproportionately high share of the global malaria burden. In 2015, the region was home to 89% of malaria cases and 91% of malaria deaths.

Malaria is caused by Plasmodium parasites. The parasites are spread to people through the bites of infected female *Anopheles* mosquitoes, called "malaria vectors." There are 5 parasite species that cause malaria in humans, and 2 of these species – *P. falciparum* and *P. vivax* – pose the greatest threat.
• *P. falciparum* is the most prevalent malaria parasite on the African continent. It is responsible for most malaria-related deaths globally.
• *P. vivax* has a wider distribution than *P. falciparum*, and predominates in many countries outside of Africa.

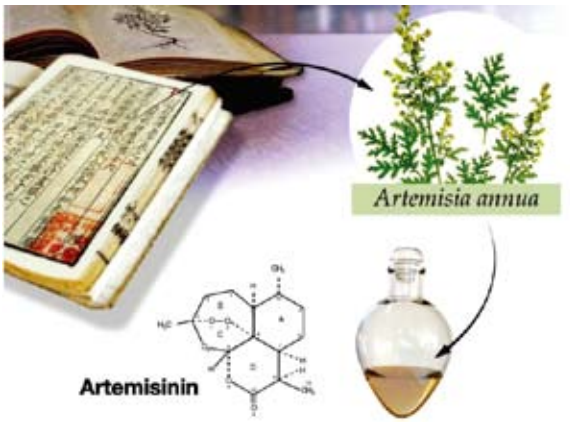
By the Numbers

Cases
214 million
malaria cases reported worldwide in 2015

Incidence
37%
global decrease in malaria incidence between 2000 and 2015

Mortality
60%
decrease in global malaria mortality rates between 2000 and 2015

Retrieved from World Health Organization Malaria fact sheet (http://www.who.int/malaria/en/, http://www.who.int/mediacentre/factsheets/fs094/en/)



As one of the over 500 researchers involved in "Project 523", a government solicitation across the country for a new antimalarial drug, TU was inspired by a classic of traditional Chinese medicine called *Handbook of Prescription for Emergency*, which was written by a famous alchemist GE Hong in the Eastern Jin Dynasty. She came to know that sweet wormwood could serve as a cure for Malaria. The main idea was to soak a handful of the plant with two liters of water, extract the juice by twisting, and then drink it all.

great interest to future scientific research.

Apparently, such a structure is the key to understanding the working mechanism of artemisinin. By far, scientists have remarkably advanced their knowledge on the role of the ring's peroxide bridge, for example, and published many high quality papers on the subject.

Also, the structure may have two other important applications than malaria treatment, researchers found. One owes to its antitumor potential, the other to its therapeutic effect against immune system diseases. A new drug based on artemisinin developed at SIMM for treating lupus erythematosus is currently going through a phase I clinical trial.

Meanwhile, it also shed light on new ways of synthesizing artemisinin drugs. Sweet wormwood is traditionally grown in large areas in western China's Sichuan Province. However, such plantations usually take up a lot of land, the extraction of artemisinin costs large amounts of solvents, and the chemical wastes produced pose a constant threat to local environment. It would be much more efficient if artemisinin could be synthesized from scratch using just chemical materials and chemical reactions. Scientists in and outside China are now working on this idea, and as far as I know, they are very likely to collaborate and together find a complete route for the total synthesis of artemisinin.

BCAS: How do you see the controversies, triggered by this prize, over individual contribution versus collaboration in artemisinin research?

CHEN: The R&D of artemisinin won China the first Nobel Prize in sciences. Although there have been a lot of discussions since the prize was announced in early October, what I just mentioned about TU's fundamental contributions have been widely accepted by the Chinese scientific community, which justifies her laureateship after all. I think she well deserves this award.

A Nobel Prize is usually conferred to no more than three people. This year's Nobel Prize in Physiology or Medicine was shared by two separate studies, and the part concerning artemisinin went to TU alone. It is appropriate because Nobel prizes are designed to honor those forerunners who have done a ground-breaking job in their field. TU is one of such forerunners.

But let's not forget about the work of others, too. It is fair to say that had artemisinin drugs been confined to their primitive status, say as a suppository, it would never have become so important and beneficial to the world. Like I said, researchers from CAS contributed significantly to the structural analysis as well as the discovery, synthesis and study of artemether. And for that matter, LI Guoqiao from Guangzhou University of Traditional Chinese Medicine played a key role in the clinical tests of the drugs. The contribution of these researchers should not be forgotten by the scientific community and ordinary people.

In fact, prior to the Nobel Prize, China's artemisinin research had bagged many other awards. For instance, in 1996 as a team, it received the Qiu Shi Outstanding Scientific Research Team Award from Hong Kong. In 2003, the team was recognized for the first time outside China, by the Thai government. And it is well known that in 2011 TU won the Lasker DeBakey Clinical Medical Research Award because of her pioneering role in the artemisinin research.

BCAS: Artemisinin research makes a role model of scientific collaboration. Do you think we can somehow learn from this success story to boost today's research efficiency in China?

CHEN: First I'd like to emphasize that TU's role in artemisinin research was pioneering and that she opened the ground for all subsequent studies. But without group efforts, today's achievement would have been impossible. That was what TU told her audience when she received the Lasker Award in 2011.

The collaboration came to a great success because it was conducted between the late 1960s and the1970s, a special period of time when collectivism was highly valued and individuality and personal interests were neglected. As a result, such a basic study straddling many disciplines and organizations progressed with little difficulties. Frankly,

such a "whole nation system" can hardly be relived in today's China.

Nevertheless, there are many experiences to learn from this part of the history. Given the research conditions much lagging behind at that time, collaboration was the only key to success. There are so many things we need to think about for today. Our current research system is pieced up by small teams with a principal investigator plus a handful of members. And our evaluation system may push a researcher towards "being the head of a chicken rather than the tail of a cow". These practices are undermining the basic spirit of cooperation.

BCAS: TU claimed that artemisinin is "a gift to the people of the world from TCM". However, the Nobel Prize committee said "we are NOT giving a prize to the traditional medicine". What is your opinion?

CHEN: I see what the committee meant by saying that. Nobel Prizes never honor a certain discipline or field, but a specific research subject. So this prize actually went to artemisinin research, not TCM.

But I also agree when the committee said that although the prize is not for traditional medicine, TU has been "inspired" by it. If she had not read GE Hong's book, she wouldn't have come up with the idea in the first place, not to mention finding the right way to isolate artemisinin and developing it to drugs.

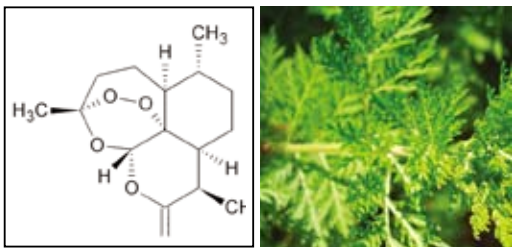
So to some extent, this can be seen as a modern confirmation of the validity of TCM. In fact, there are numerous such cases in which scientists gain initial inspiration from ancient literature and then use modern techniques to reveal the material basis of the medicinal effects. There is no doubt that TCM has been contributing a lot to human welfare, especially the welfare of Chinese people. And I believe that along with this Nobel Prize, great opportunities will come for the modernization and internationalization of the entire TCM business in China.

BCAS: What are the challenges for the modernization of TCM?

CHEN: The challenges, on one hand, lie in the identification of the material basis and working mechanism of the medicine; on the other, the standardization of drug quality.

We are still unable to answer fundamental questions like: what are the substances (or active ingredients) that actually work in a particular kind of traditional medicine, and how do they work? For instance, for the same type of herb, it is effective on some people and not on others. Why? That could come from the genetic differences

Artemisinin



(Left) Chemical structure of artemisinin (*Credit: Lukáš Mižoch*) **(Right)** *Artemisia annu*, or sweet wormwood, from which artemisinin is isolated.

Artemisinin, also known as ***qinghaosu***, and its semi-synthetic derivatives are a group of drugs that possess the most rapid action of all current drugs against *Plasmodium falciparum* malaria. It was discovered by Tu Youyou, a Chinese scientist, who was awarded half of the 2015 Nobel Prize in Medicine for her discovery. Treatments containing an artemisinin derivative (artemisinin-combination therapies, ACTs) are now standard treatment worldwide for *P. falciparum* malaria. Artemisinin is isolated from the plant *Artemisia annua*, sweet wormwood, an herb employed in Chinese traditional medicine. A precursor compound can be produced using genetically engineered yeast.

Chemically, artemisinin is a sesquiterpene lactone containing an unusual peroxide bridge. This peroxide is believed to be responsible for the drug's mechanism of action. Few other natural compounds with such a peroxide bridge are known.

Artemisinin and its endoperoxides derivatives have been used for the treatment of *P. falciparum* related infections but low bioavaibility, poor pharmacokinetic properties and high cost of the drugs are a major drawback of their use. Use of the drug by itself as a monotherapy is explicitly discouraged by the World Health Organization, as there have been signs that malarial parasites are developing resistance to the drug. Therapies that combine artemisinin or its derivatives with some other antimalarial drug are the preferred treatment for malaria and are both effective and well tolerated in patients. The drug is also increasingly being used in Plasmodium vivax malaria, as well as being a topic of research in cancer treatment. (From Wikipedia: https://en.wikipedia.org/wiki/Artemisinin)

As a co-winner of the 2015 Nobel Prize in Physiology or Medicine, TU, at the age of 84, received her Nobel medal, diploma and a document confirming the prize amount from King XVI Gustaf of Sweden at the Stockholm Concert Hall on December 10, 2015.

between patients. It could also be attributed to the climate and location in which the herb is grown. *Astragalus* from Shandong does not have the exact same efficacy with that from Shanxi. Even for plants cultivated in the same area, their compositions may vary during dry and wet seasons. These are the first things we need to elucidate before talking about the modernization and internationalization of TCM.

Partly due to this reason, there has been an absence of quality control and standardization since the very beginning of TCM. In my opinion, quality control of TCM should aim at both the effectiveness and safety of drugs. People used to say that TCM is natural and harmless. This is a big misunderstanding; many natural substances are really toxic. It is said that when Shennong, the legendary originator of Chinese herbal medicine, was trying out medicinal plants by tasting them one by one, he ended up getting poisoned seventy times a day.

However, I am quite confident about the future of TCM. I would like to mention a paper published in *Science* magazine last February by German and US researchers, who reported a small molecule tetrandrine, an ingredient from traditional Chinese medicine as an effectively inhibitor against the entry of Ebola virus into host cells. This is another example showing how TCM could be used to address the world's major health threats for the benefit of the mankind.