Artemisinin: against viruses, cancer and malaria

Chemist Professor Dr Svetlana B Tsogoeva and biologists Professors Drs Thomas Efferth and Manfred Marschall are collaborating on a project to develop new straightforward synthetic methods for creating antiviral, antimalarial and anticancer agents using artemisinin and its semi-synthetic derivatives.

Can you discuss what inspired you to pursue a career in medicinal chemistry and outline the beginnings of your current project?

SBT: During my doctoral studies in the fields of bioorganic and medicinal chemistry at St. Petersburg State University in Russia, I was completely obsessed with my scientific work and loved what I did. After obtaining a PhD in 1998, I wanted to focus my efforts on developing efficient natural product-derived anticancer agents, since cancer was and still is one of the leading causes of mortality worldwide.

In 2002, I started my independent research work at Gottingen University in Germany aiming to connect two powerful research directions: organocatalysis and medicinal chemistry. My long-term goal is to develop environmentally friendly and sustainable organocatalytic methods towards bioactive compounds and anticancer, antiviral and antimalarial agents. This is one of the current research topics in my group at the University of Erlangen-Nurnberg (FAU), which we are investigating in collaboration with biologists and physicians. Our particular focus is on the natural product artemisinin, which was introduced to my research group in 2004 by expert in phytomedicine Professor Thomas Efferth (University of Mainz). In the same year, we began our fruitful collaboration in developing artemisinin-derived anticancer and antimalarial agents. In 2013, we started further rewarding cooperative work with a virology expert Professor Manfred Marschall (FAU).

Artemisinin is extracted from a Chinese medicinal plant and has been shown to be a versatile antimalarial, anticancer and antiviral compound. What are the properties that enable its diverse applications?

SBT: Over the years, meta-analyses of malaria patients treated with artemisinin have demonstrated the high efficacy and safety of this class of drugs. However, despite its overwhelming antimalarial activity, the true potential of artemisinin was underestimated in the Western world for many years. It was only recently that the high value of the artemisinin group of compounds, including its usefulness for ongoing drug development, has been recognised. Although the mechanism of action of artemisinin is still not completely understood, it is generally accepted that the endoperoxide bridge within the 1,2,4 trioxane system is essential for its activity. In particular, in the cases of malaria and cancer, the endoperoxide moiety can be activated and fragmented by intracellular Fe(II), leading to the formation of reactive oxygen species and peroxyl free radicals. These species induce oxidative stress, DNA damage, alkylation of target proteins and apoptosis.

Could you discuss some of the difficulties presented by drug resistance to artemisinin?

TE: Resistance to artemisinin is still a rare event and cannot be compared with the frequent resistance phenomena seen with other drugs. If artemisinin resistance occurs, it is multifactorial. There is not a single mechanism that satisfactorily explains delayed killing of malaria parasites. It can be questioned, whether or not delayed killing of plasmodia can be called resistance, because a full-blown resistance phenotype against artemisinin has not been identified thus far. Delayed response of plasmodia to artemisinin has been observed with a lot of panic and hysteria. This so-called ‘resistance’ has been overestimated. It remains to be seen whether or not true resistance phenomena regarding artemisinin will appear.

To what extent does your work differ from other research projects involving the use of artemisinin to combat disease?

SBT: Traditionally, the synthesis of artemisinin-derived drug candidates requires multistep synthesis with isolation and purification of product intermediates and, in most cases, metal-based catalysts are used for chemical transformations. My research group strives to develop more facile and atom economic synthetic methods employing organocatalysis, and which can be performed in one-pot reactions without the involvement of time- and cost-consuming, and waste-producing isolation and purification steps.
From traditional cures to novel treatments

Researchers from the University of Erlangen-Nuremberg are creating effective and sustainable multistep domino reactions for generating, in a single operation, novel artemisinin-derived agents that could lead to new treatments against a range of diseases.

Artemisinin is a term denoting a group of compounds derived from the plant Artemisia annua L., a herb used in traditional Chinese medicine. Its discovery emerged from a drug screening programme launched by the Chinese Government during the Vietnam War with the aim of finding new antimalarial compounds. Having discovered artemisinin in 1972, Chinese scientist Tu Youyou was co-awarded the Nobel Prize in Physiology or Medicine only in 2015. Therefore, despite its evident antimalarial properties, the scope and potential of the natural product has only recently been truly recognised.

Hybridisation involves the manipulation of artemisinin by applying combinations of several natural product fragments to create new structures that possess improved properties.

Artemisinin derivatives

Given the overwhelming evidence for artemisinin’s effectiveness in the treatment of malaria – having been administered since clinical trials in the 1970s – it has more recently been explored in the context of other diseases. More specifically, a team led by Professor Dr Svetlana B Tsogoeva is dedicated to developing environmentally friendly synthetic methods of producing artemisinin-based anticancer, antiviral and antimalarial agents in close collaboration with experts in the biological sciences.

The researchers are looking at a means of preventing drug resistance to the class of compounds by designing and synthesising novel and highly active artemisinin derivatives. “A remarkable advantage of artemisinin and its semi-synthetic analogue arteunate lies in their low toxicity to normal cells. The applicability of artemisinin as a drug is, however, limited by its low solubility and poor oral bioavailability,” explains Tsogoeva. “To develop even more effective drug candidates than artemisinin and arteunate, we apply an already established chemical hybridisation concept.”

The hybridisation process used by the team involves the manipulation of artemisinin by applying combinations of several natural product fragments to create new structures that possess improved properties in comparison to their parent compounds.

Cancer, viruses and malaria

The research group has designed and synthesised a wide variety of artemisinin-derived dimers and hybrids through the use of different chemical linkers. Findings have shown that the products of their designs are far more potent against cancer, viruses and malaria. “The nature and length of the linker in a hybrid drug is crucial, and might also be partially responsible for the biological effect,” explains Tsogoeva. “Hybrid molecules can have bifunctional or even multifunctional activities and, therefore, cooperative and synergistic effects.”

Tsogoeva and her collaborators have identified a key area for future investigations; namely, identifying the most important cellular mechanisms and molecular pathways regulated when their artemisinin-derived dimers and hybrids are used.

A domino effective

The originality of the team’s research lies in the fact that the hybrid products are created through a single operation, using sustainable one-pot multistep domino reactions to form nitrogen-containing bioactive heterocyclic compounds connected to artemisinin moieties. Indeed, one notable finding is an unprecedented step forward. “We reported an organocatalytic two component six-step domino reaction, generating new artemisinin-derived compounds with strong antiviral properties that outperform clinically used ganciclovir,” enthuses Tsogoeva.

Achieving this result in a single operation is a genuinely exciting discovery and bodes well for the future. The team’s research endeavours moving forward will look to create new libraries of artemisinin-derived hybrid molecules and hybrids of different bioactive compounds with improved antiviral, anticancer and antimalarial properties.

Team members

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Funding

German Research Foundation (DFG)

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Svetlana B Tsogoeva studied Chemistry at St. Petersburg State University and was a postdoc at Goethe University of Frankfurt and a junior professor at Gottingen University. Since 2007, she has been Professor of Organic Chemistry at the University of Erlangen-Nuremberg. Her research is mainly focused on organocatalytic synthesis of antiviral, anticancer and antimalarial agents.