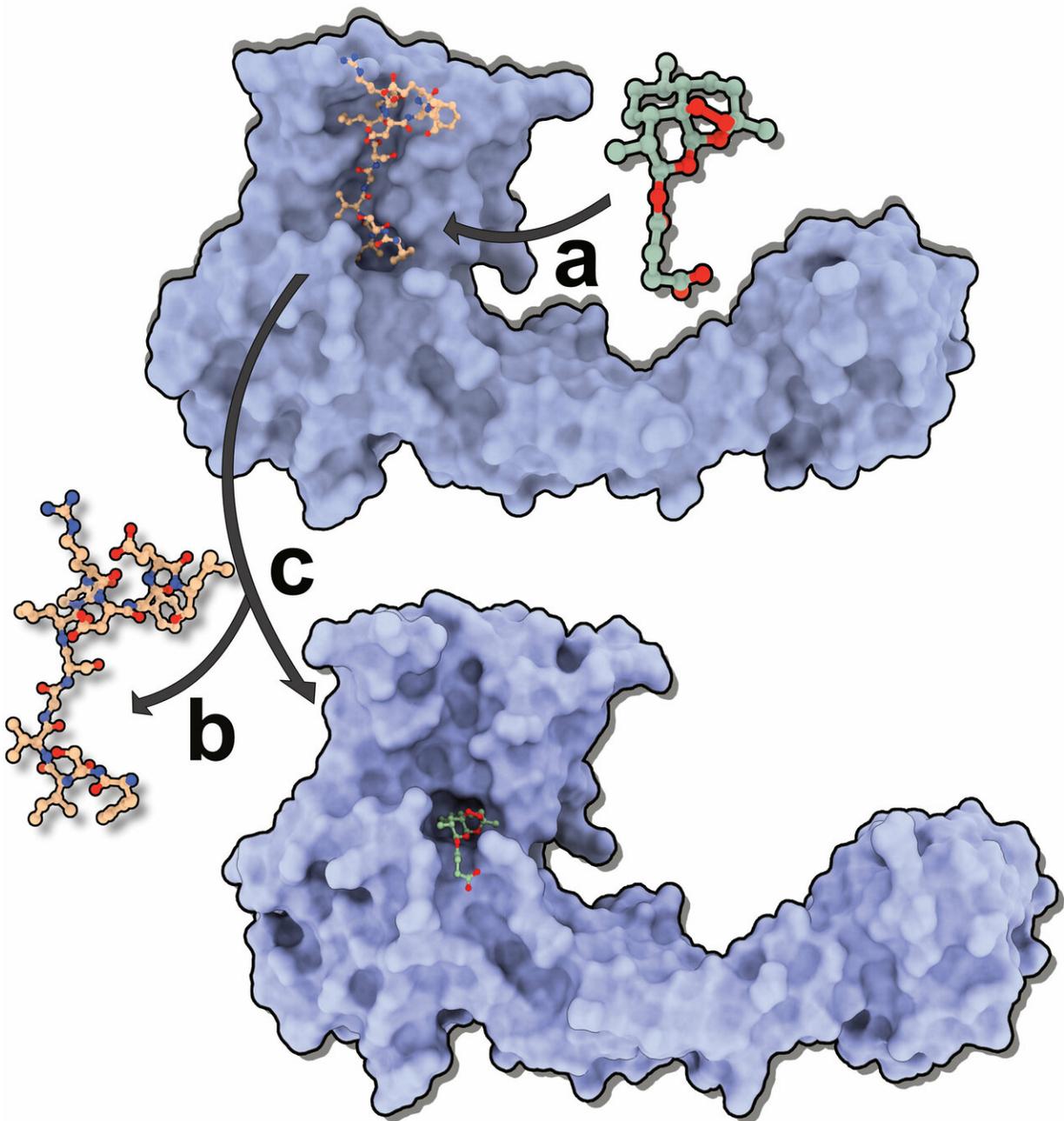


New anti-malaria drug findings reported

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Schematic representation of the formation of gephyrin-artemisinin complex.
Credit: Dr. Vikram Kasaragod, Rudolf Virchow Center

Artemisinin is derived from the leaves and flowers of the annual mugwort (*Artemisia annua*), and has been used in traditional Chinese medicine for centuries. Chinese researcher Tu Youyou recently tested its effectiveness, winning the Nobel Prize in 2015. Artemisinin and its semi-synthetic derivatives—collectively known as artemisinins—are used to treat the tropical infectious disease malaria. In addition, these molecules influence multiple cellular processes in humans. For example, artemisinins activate the immune system against several types of cancer and regulate the differentiation of pancreatic T cells, which could potentially be useful in the therapy of diabetes.

"Although this clinically-approved drug class is well established and has been used to some extent for centuries, it was unclear which [molecular mechanisms](#) underlie the corresponding cellular activities," explains Dr. Vikram Kasaragod. The postdoctoral fellow in the research group of Professor Hermann Schindelin at the Rudolf Virchow Center is the first author of the study, now published in the journal *Neuron*.

The structural biologist was the first to solve the crystal structures of two different artemisinin derivatives—artesunate and artemether—in a complex with gephyrin. By binding to inhibitory glycine and GABAA receptors, gephyrin acts as a central scaffold protein of inhibitory postsynapses in the mammalian central nervous system. Gephyrin has only recently been identified as an artemisinin target protein. The results clearly demonstrate that artemisinins target the universal receptor binding pocket in gephyrin and compete with the inhibitory

neurotransmitter receptors for an overlapping binding site. These new findings could thus also serve as an effective tool to understand the physiology of the human brain.

According to Kasaragod, the crystal structures, together with biochemical, electrophysiological and in vivo data, form a comprehensive model of the regulation of inhibitory neurotransmission by artemisinin. This model clearly describes the interactions between proteins and drugs.

"Our data not only provide a solid foundation for understanding how artemisinins are recognized by a target molecule, but will also help researchers to develop and optimize these agents into highly specific modulators of gephyrin. These modulators may play an important role in the treatment of neurological diseases such as Alzheimer's disease, schizophrenia and epilepsy," says Schindelin, the lead investigator.

More information: Vikram Babu Kasaragod et al, Elucidating the Molecular Basis for Inhibitory Neurotransmission Regulation by Artemisinins, *Neuron* (2019). [DOI: 10.1016/j.neuron.2019.01.001](https://doi.org/10.1016/j.neuron.2019.01.001)

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