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Targeted anticancer drug discovery based on natural product derivitives

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Anti-malaria natural product artemisinin (Qinghaosu) has been repositioned for the development of novel antitumor agents due to its unique structure and safety profile. Nevertheless, compared to the great success in the development of anti-malarial drugs, the majority of reported artemisinin analogues (artemalogues) only displayed limited in vitro and in vivo anticancer potency. In addition, the precise anticancer mechanism of these artemalogues) are also poorly understood. Therefore, chemical modification on artemisinin is highly needed both for the development of more potent anticancer artemalogues and for the understanding of the mode of actions. Most of the reported structural modifications focuse on the C10-carbonyl function with the aim to enhance the pharmacokinnetical properties. To generate structurally more diverse artemalogues, we conducted an alternative medicinal chemistry campaign by constructing various heterocyclic functionalities at the less explored sites including C-6 and -9 positions through 1,3-dipolar cycloaddition or click reaction, thus affording a series of structurally novel artemalogues. Several compounds demonstrated superior *in vitro* antiproliferative effects against cancer cell lines with IC_{50} values in nanomolar ranges. We further investigated the effects of artemisinin and three potent artemalogues on protein expression in whole A549 cells by using mass spectrometry-based global chemical proteomics approach, and systematically identified dozens of significantly up- and down-regulated proteins through quantitative proteomic analysis, some of which are involved in essential biological processes. These findings will shed light on the understanding of anticancer action mechanism of artemalogues.

Biography:

Professor Zhang received the Ph.D. diploma in 2000, and did Postdoctoral research at Georgetown University and Harvard Medical School during 2002-2004. He was promoted to Instructor of Harvard Medical School in 2004 and received the Hundred Talent Project award from the Chinese Academy of Sciences, and became the Professor of Medicinal Chemistry at Shanghai Institute of *Materia Medica* (SIMM). In 2011, he was awarded the Distinguished Young Investigator Award from Chinese Natural Science Foundation. He has authored or co-authored over 110 publications and 40 patents. Several drug candidates from his research group are now under clinical or preclinical studies.