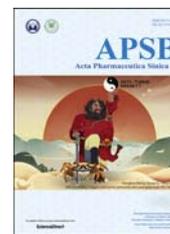




Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



Graphical Abstracts/Acta Pharmaceutica Sinica B, 9 (2019) iii–ix

Reviews

Acta Pharmaceutica Sinica B, 9 (2019) 203

Repurposing vitamin D for treatment of human malignancies via targeting tumor microenvironment

Xu Wu^a, Wei Hu^b, Lan Lu^c, Yueshui Zhao^a, Yejiang Zhou^d, Zhangang Xiao^a, Lin Zhang^{a,c}, Hanyu Zhang^a, Xiaobing Li^a, Wanping Li^a, Shengpeng Wang^f, Chi Hin Cho^a, Jing Shen^a, Mingxing Li^a

^aLaboratory of Molecular Pharmacology, Department of Pharmacology, School of Pharmacy, Southwest Medical University, Luzhou 646000, China

^bDepartment of Gastroenterology, Shenzhen Hospital, Southern Medical University, Shenzhen 518000, China

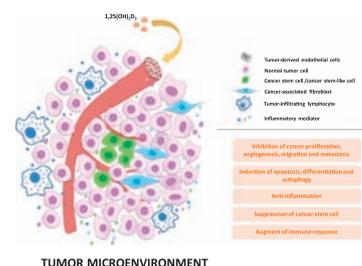
^cSichuan Industrial Institute of Antibiotics, Chengdu University, Chengdu 610106, China

^dDepartment of Gastrointestinal Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, China

^eDepartment of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China

^fState Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao, China

Supplementation of vitamin D is associated with reduced cancer risk and favorable prognosis. Vitamin D not only suppresses cancer cells and cancer stem cells, but also regulates tumor microenvironment, demonstrating the promise of the benefit of vitamin D in cancer prevention and treatment.



TUMOR MICROENVIRONMENT

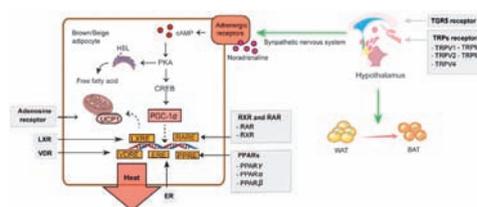
Acta Pharmaceutica Sinica B, 9 (2019) 220

Small molecules for fat combustion: targeting obesity

Jingxin Liu, Yitao Wang, Ligen Lin

State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Taipa 999078, Macau, China

Brown adipose tissue (BAT) and beige cells dissipates fatty acids as heat, termed non-shivering thermogenesis, which has emerged as a potential therapeutically way to treat obesity. The current review provides a comprehensive and up-to-date of knowledge from the biological importance of thermogenesis to the representative thermogenic regulators for treating obesity.



Acta Pharmaceutica Sinica B, 9 (2019) 237

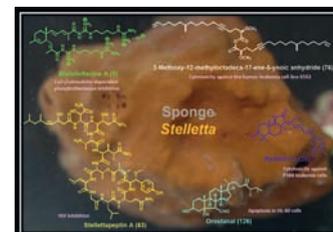
Marine sponges of the genus *Stelletta* as promising drug sources: chemical and biological aspects

Qihao Wu^{a,b}, Bastien Nay^c, Min Yang^a, Yeke Ni^a, Hong Wang^b, Ligong Yao^a, Xuwen Li^a

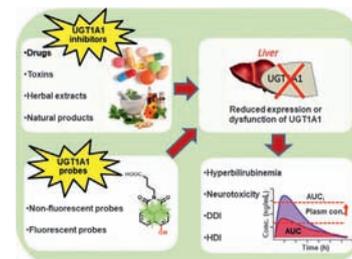
^aState Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Zhangjiang Hi-Tech Park, Shanghai 201203, China

^bCollege of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, China

^cLaboratoire de Synthèse Organique (UMR 7652 CNRS), Ecole Polytechnique, Université Paris-Saclay, 91128 Palaiseau Cedex, France



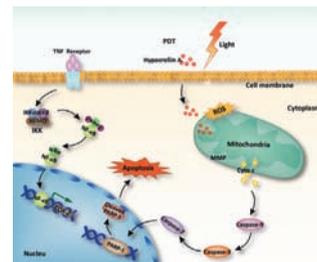
Marine sponges of the genus *Stelletta* are well known as rich sources of diverse and complex natural products with novel structures and broad biological activities, which have attracted a lot of attention from chemists seeking to perform their total synthesis in parallel to intensive biological studies towards new drug leads. In this review, we summarize the chemical and biological aspects of *Stelletta* sponges as promising drug sources.

Recent progress and challenges in screening and characterization of UGT1A1 inhibitorsXia Lv^{a,b}, Yangliu Xia^c, Moshe Finel^d, Jingjing Wu^c, Guangbo Ge^{a,c}, Ling Yang^a^a*Institute of Interdisciplinary Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China*^b*Key Laboratory of Biotechnology and Bioresources Utilization, Ministry of Education, College of Life Science, Dalian Minzu University, Dalian 116600, China*^c*Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China*^d*Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Finland*

Strong inhibition of UGT1A1 may not only trigger clinical adverse drug/herb–drug interactions (D/HDI), but also result in metabolic disorders *via* modulation of endobiotic metabolism. This review focuses on the significance, progress and challenges in the discovery and characterization of UGT1A1 inhibitors, as well as the recent advances in the development of UGT1A1 probe substrates for screening and characterization of UGT1A1 inhibitors.

Original Articles**Hypocrellin A-based photodynamic action induces apoptosis in A549 cells through ROS-mediated mitochondrial signaling pathway**Shanshan Qi^{a,b}, Lingyuan Guo^a, Shuzhen Yan^a, Robert J. Lee^b, Shuqin Yu^c, Shuanglin Chen^a^a*Jiangsu Province Key Laboratory for Microbes and Functional Genomics, College of Life Sciences, Nanjing Normal University, Nanjing 210023, China*^b*College of Pharmacy, the Ohio State University, Columbus, OH 43210, USA*^c*Jiangsu Province Key Laboratory for Molecular and Medical Biotechnology, College of Life Sciences, Nanjing Normal University, Nanjing 210023, China*

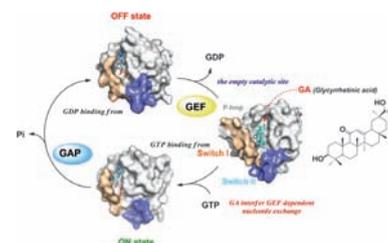
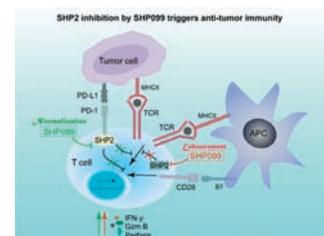
Hypocrellin A-mediated oxidative injury induced by light emitting diode irradiation triggers mitochondrial membrane potential changes and dysfunction, then mitochondrial cytochrome *c* release and caspase activation, which consequently lead to apoptosis. The study demonstrated hypocrellin A may be a possible therapeutic anticancer agent directed toward mitochondria.

**Glycyrrhetic acid binds to the conserved P-loop region and interferes with the interaction of RAS-effector proteins**

Yuan Zhang, Zhihua Wang, Xiaoyao Ma, Shengnan Yang, Xueyan Hu, Jin Tao, Yuanyuan Hou, Gang Bai

State Key Laboratory of Medicinal Chemical Biology, College of Pharmacy and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin 300353, China

Glycyrrhetic acid binds to the conserved P-loop region of RAS protein, induces a conformational change, and alters its stability. Meanwhile, glycyrrhetic acid abolishes the function of RAS by interfering with the effector protein RAF kinase activation and RAS/MAPK signalling.

**SHP2 inhibition triggers anti-tumor immunity and synergizes with PD-1 blockade**Mingxia Zhao^a, Wenjie Guo^a, Yuanyuan Wu^b, Chenxi Yang^a, Liang Zhong^c, Guoliang Deng^a, Yuyu Zhu^a, Wen Liu^a, Yanhong Gu^d, Yin Lu^b, Lingdong Kong^a, Xiangbao Meng^{a,c}, Qiang Xu^a, Yang Sun^a^a*State Key Laboratory of Pharmaceutical Biotechnology, Department of Biotechnology and Pharmaceutical Sciences, School of Life Sciences, Nanjing University, Nanjing 210023, China*^b*Jiangsu Key Laboratory for Pharmacology and Safety Evaluation of Chinese Materia Medica, School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, China*^c*State Key Laboratory of Natural and Biomimetic Drugs, Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China*^d*Department of Oncology, the First Affiliated Hospital with Nanjing Medical University, Nanjing 210029, China*

The SHP2 allosteric inhibitor, SHP099, is a promising drug candidate for cancer immunotherapy. SHP2 inhibition both enhances and normalizes anti-tumor immunity, and the combination of SHP099 and anti-PD-1 is a potentially robust therapeutic strategy for cancer control.

The epigallocatechin gallate derivative Y₆ reverses drug resistance mediated by the ABCB1 transporter both *in vitro* and *in vivo*

Yan Wen^{a,b,c}, Ruiqiang Zhao^{a,d}, Pranav Gupta^a, Yingfang Fan^{a,c}, Yunkai Zhang^a, Zhenguang Huang^b, Xiaohui Li^f, Yuangang Su^f, Lijuan Liao^f, Yu-An Xie^g, Donghua Yang^a, Zhe-Sheng Chen^a, Gang Liang^h

^aDepartment of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, Queens, NY 11439, USA

^bDepartment of Pharmacy, the First Affiliated Hospital of Guangxi Medical University, Nanning 530021, China

^cGuangxi Colleges and Universities Key Laboratory of Biological Molecular Medicine Research, Guangxi Medical University, Nanning 530021, China

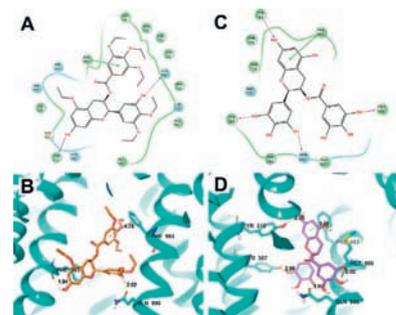
^dDepartment of Biochemistry and Molecular Biology, School of Preclinical Medicine, Guangxi Medical University, Nanning 530021, China

^eDepartment of Hepatobiliary Surgery, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, China

^fDepartment of Biotechnology, School of Preclinical Medicine, Guangxi Medical University, Nanning 530021, China

^gThe Affiliated Tumor Hospital of Guangxi Medical University, Nanning 530021, China

^hCollege of Pharmacy, Guangxi Medical University, Nanning 530021, China



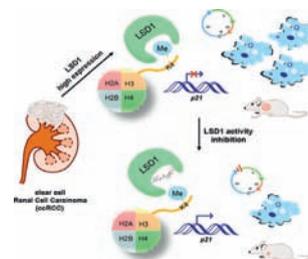
Y₆, an epigallocatechin gallate derivative, reverses ABCB1-mediated multidrug resistance *in vitro* and *in vivo*, and the reversal effect of Y₆ is significantly greater than epigallocatechin gallate.

LSD1 inhibition suppresses the growth of clear cell renal cell carcinoma *via* upregulating P21 signaling

Liangsong Zhu, Jianfeng Wang, Wen Kong, Jiwei Huang, Baijun Dong, Yiran Huang, Wei Xue, Jin Zhang

Department of Urology, Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200127, China

Histone lysine-specific demethylase1 (LSD1) mediates cell proliferation in clear cell renal cell carcinomas (ccRCC). LSD1 is highly expressed in ccRCC samples and it suppresses H3K4 methylation, inducing ccRCC cell proliferation through P21 signaling dysfunction; inhibition of LSD1 restores H3K4 methylation, inducing G1/S cell-cycle arrest by increasing the level of check-point regulator P21.



Design, synthesis and biological evaluation of chalcone analogues with novel dual antioxidant mechanisms as potential anti-ischemic stroke agents

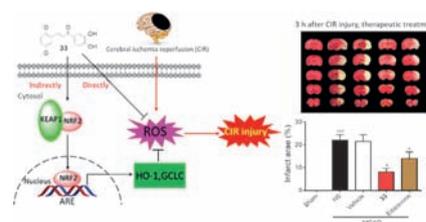
Jiabing Wang^{a,b}, Lili Huang^{a,c}, Chanchan Cheng^a, Ge Li^a, Jingwen Xie^a, Mengya Shen^a, Qian Chen^a, Wulan Li^{a,d}, Wenfei He^a, Peihong Qiu^a, Jianzhang Wu^a

^aChemical Biology Research Center, School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou 325035, China

^bMunicipal Hospital Affiliated to Medical School of Taizhou University, Taizhou 318000, China

^cNingbo Medical Centre Li Huili Hospital, Ningbo 315041, China

^dCollege of Information Science and Computer Engineering, Wenzhou Medical University, Wenzhou 325035, China



Chalcone analogue **33** conferred protection of PC12 cells against H₂O₂ insult with novel dual-antioxidant mechanism of directly scavenging reactive oxygen species (ROS) and indirectly through antioxidant pathway activation, and the effect of **33** was more pronounced than that of mono-antioxidant mechanism compounds after MCAO and BSAO in animals.

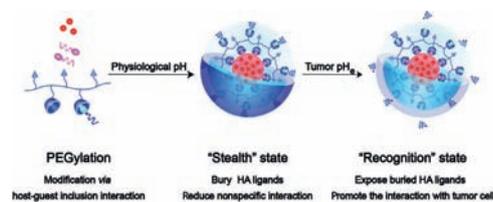
Transformative hyaluronic acid-based active targeting supramolecular nanoplatform improves long circulation and enhances cellular uptake in cancer therapy

Lu Zhong^a, Lu Xu^a, Yanying Liu^a, Qingsong Li^a, Dongyang Zhao^a, Zhenbao Li^a, Huicong Zhang^a, Haotian Zhang^b, Qiming Kan^b, Yongjun Wang^a, Jin Sun^a, Zhonggui He^a

^aDepartment of Pharmaceutics, Wuya College of Innovation, Shenyang Pharmaceutical University, Shenyang 110016, China

^bDepartment of Pharmacy, Shenyang Pharmaceutical University, Shenyang 110016, China

The transformative CD44-targeted hyaluronic acid (HA) supramolecular nanoplatform would keep the "stealth" state in the blood stream due to the buried HA and the reduced interaction with biosystem by PEG shell. Then the nanoparticles could transform into the "recognition" state for improving cellular uptake *via* HA-mediated endocytosis after removing the "stealth" PEG layer and exposing the buried HA ligands at the tumor microenvironment pH.



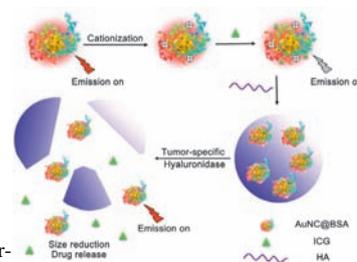
Theranostic nanoparticles with tumor-specific enzyme-triggered size reduction and drug release to perform photothermal therapy for breast cancer treatment

Rui Liu^a, Chuan Hu^a, Yuanyuan Yang^a, Jingqing Zhang^b, Huile Gao^a

^aKey Laboratory of Drug Targeting and Drug Delivery System of the Education Ministry, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

^bChongqing Research Center for Pharmaceutical Engineering, Chongqing Medical University, Chongqing 400016, China

The simply-constructed size-reducible AuNC@CBSA-ICG@HA could be degraded by tumor-specific hyaluronidase into small particles for deep penetration and drug release in tumor region, thus homogeneously distributing in tumor and locally releasing therapeutic agents. The investigations of double locations of carrier and drug provided many opportunities for AuNC@CBSA@HA loading other drugs.



Redox-sensitive prodrug nanoassemblies based on linoleic acid-modified docetaxel to resist breast cancers

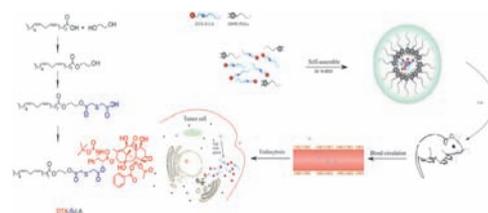
Meng Li^a, Liwen Zhao^a, Tao Zhang^a, Yue Shu^a, Zhonggui He^a, Yan Ma^c, Dan Liu^b, Yongjun Wang^a

^aWuya College of Innovation, Shenyang Pharmaceutical University, Shenyang 110016, China

^bKey Laboratory of Structure-Based Drug Design and Discovery, Ministry of Education, Shenyang Pharmaceutical University, Shenyang 110016, China

^cSchool of Chinese Materia Medica, Guangzhou University of Chinese Medicine, Guangzhou 510405, China

A novel prodrug was designed and synthesized which utilized mono thioether bond as a linker to bridge linoleic acid and docetaxel. This redox sensitive conjugate could self-assemble into nanoparticles which had excellent physical stability, strong cytotoxic activity, prolonged circulation time and enhanced anticancer efficacy.



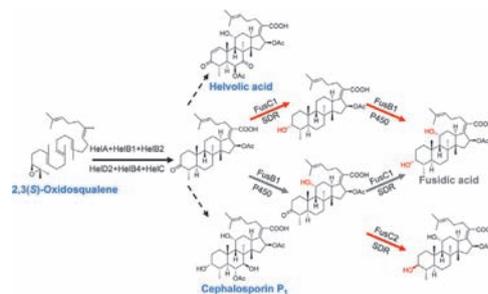
Biosynthesis of clinically used antibiotic fusidic acid and identification of two short-chain dehydrogenase/reductases with converse stereoselectivity

Zhiqin Cao^a, Shaoyang Li^a, Jianming Lv^a, Hao Gao^a, Guodong Chen^a, Takayoshi Awakawa^b, Ikuro Abe^b, Xinsheng Yao^a, Dan Hu^a

^aInstitute of Traditional Chinese Medicine and Natural Products, College of Pharmacy/Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, Jinan University, Guangzhou 510632, China

^bGraduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Fusidane-type antibiotics, represented by fusidic acid, helvolic acid and cephalosporin P₁, are a group of fungi-derived triterpenoid antibiotics. Here, we firstly identified the biosynthetic gene cluster of the clinically used fusidic acid and characterized its full biosynthetic pathway using a combinational biosynthetic approach. Notably, we identified two short-chain dehydrogenase/reductase FusC1 and FusC2 with converse stereoselectivity in 3-ketoreduction.



Meeting Report

Acta Pharmaceutica Sinica B, 9 (2019) 443

Highlights of the 2nd International Symposium on Tribbles and Diseases: tribbles tremble in therapeutics for immunity, metabolism, fundamental cell biology and cancer

Bing Cui^a, Patrick A. Eyers^b, Leonard L. Dobens^c, Nguan Soon Tan^{d,e,f,g}, Peter D. Mace^h, Wolfgang A. Link^{i,j,k}, Endre Kiss-Toth^l, Karen Keeshan^m, Takuro Nakamuraⁿ, Warren S. Pear^o, Yodit Feseha^{p,q}, Jessica Johnston^l, Arkatiz Carracedo^{r,s,t,u}, Marcel Scheideler^{v,w,x,y}, Zabrán Ilyas^l, Robert C. Bauer^z, Jorge D. Erusalimsky^{aa}, Dominika Grzesik^{ab}, Juan Salamanca-Viloria^{ac,ad}, Xiaoxi Lv^a, Yishi Jin^{ae}, Ke Li^{a,af}, Guillermo Velasco^{ag}, Shuang Shang^a, Jose M. Lizcano^{ah}, Xiaowei Zhang^a, Jichao Zhou^a, Jiaojiao Yu^a, Fang Hua^a, Feng Wang^a, Shanshan Liu^a, Jinmei Yu^a, Zhuowei Hu^a

^aState Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China

^bDepartment of Biochemistry, Institute of Integrative Biology, University of Liverpool, Liverpool L69 7ZB, UK

^cDivision of Molecular Biology and Biochemistry, School of Biological Sciences, University of Missouri-Kansas City, Kansas City, MO 64110, USA

^dSchool of Biological Sciences, Nanyang Technological University, Singapore 637551, Singapore

^eLee Kong Chian School of Medicine, Nanyang Technological University, Singapore 639798, Singapore

^fInstitute of Molecular and Cell Biology, Singapore 138673, Singapore

^gKK Women's and Children Hospital, Singapore 229899, Singapore

^hBiochemistry Department, School of Biomedical Sciences, University of Otago, Dunedin 9054, New Zealand

ⁱCentre for Biomedical Research (CBMR), University of Algarve, Campus de Gambelas, Faro 8005-139, Portugal

^jDepartment of Biomedical Sciences and Medicine, University of Algarve, Faro 8005-139, Portugal

^kAlgarve Biomedical Center (ABC), University of Algarve, Campus de Gambelas, Faro 8005-139, Portugal

^lDepartment of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield S10 2RX, UK

^mPaul O'Gorman Leukaemia Research Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland G61 1QH, UK

ⁿDivision of Carcinogenesis, The Cancer Institute, Japanese Foundation for Cancer Research, Tokyo 135-8550, Japan

^oDepartment of Pathology and Laboratory Medicine, Abramson Family Cancer Research Institute, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA

^pCentre de Recherche en Transplantation et Immunologie (ou CRTI), Inserm, Université de Nantes, Nantes, France, CHU Nantes, Nantes, France

^qInstitut de Transplantation Urologie Néphrologie (ou ITUN), CHU Nantes, Nantes, France

^rCIC bioGUNE, Bizkaia 48160, Spain

^sCIBERONC, Madrid 28029, Spain

^tIkerbasque, Basque Foundation for Science, Bilbao 48080, Spain

^uBiochemistry and Molecular Biology Department, University of the Basque Country (UPV/EHU), Bilbao 48080, Spain

^vInstitute for Diabetes and Cancer IDC, Helmholtz Center Munich, Neuherberg 85764, Germany

^wJoint Heidelberg-IDC Translational Diabetes Program, University Hospital Heidelberg, Heidelberg 85764, Germany

^xMolecular Metabolic Control, Medical Faculty, Technical University Munich, Munich 85764, Germany

^yGerman Center for Diabetes Research (DZD), Neuherberg 85764, Germany

^zDivision of Cardiology, Department of Medicine, Columbia University Irving Medical Center, New York, NY 10032, USA

^{aa}School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff CF5 2YB, UK

^{ab}Centre for Endocrinology, William Harvey Research Institute, John Vane Science Centre, Queen Mary, University of London, London EC1M 6BQ, UK

^{ac}Intelligent Pharma-Mind the Byte S.L., Barcelona 08028, Spain

^{ad}Facultat de Farmàcia, Universitat de Barcelona, Barcelona 08028, Spain

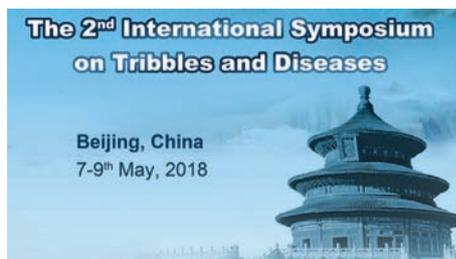
^{ae}Section of Neurobiology, Division of Biological Sciences, University of California San Diego, La Jolla, CA 92093, USA

^{af}Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100050, China

^{ag}Department of Biochemistry and Molecular Biology, School of Biology, Complutense University and Instituto de Investigaciones Sanitarias San Carlos (IdISSC), Madrid 28040, Spain

^{ah}Department of Biochemistry and Molecular Biology, Institute of Neurosciences, Faculty of Medicine, Universitat Autònoma de Barcelona, Bellaterra 08193, Spain

This is a meeting report of the 2nd International Symposium on Tribbles and Diseases held May 7–9, 2018 in Beijing, China. A group of speakers reported their recent findings and disseminated ongoing studies about Tribbles proteins related to immunity, metabolism, fundamental cell biology, cancer, and discussed potential implications for target therapy.



Cover story**Front**

Cancer immunotherapy has recently attracted much attention, which mainly features the administration of antibodies that block the so-called immune checkpoint pathways. Herein, this paper examined the effect of SHP099, an SHP2 allosteric inhibitor, on tumor growth in mouse xenograft models. We found that SHP099 decreased tumor burden *via* triggering CD8⁺ T cell-mediated anti-tumor immunity. In addition, the combination of SHP099 and anti-PD-1 antibody conferred a higher therapeutic efficacy than either monotherapy alone in controlling tumor growth. The cover paper used Chinese legendary personage Zhong Kui, the ghost buster, for reference. On one hand, anti-tumor immunity is enhanced. On the other hand, tumor growth is inhibited. This study suggests that SHP2 inhibitor SHP099 is a promising drug candidate for cancer immunotherapy.

Xiangbao Meng, Qiang Xu and Yang Sun

Back

Marine sponges are regarded as one of the most important sources of marine natural products (MNPs) with potential therapeutic applications. The sponge of the genus *Stelletta* is widely distributed in the marine ecological system, with alkaloids, triterpenoids, and peptides as its most prominent bioactive secondary metabolites. The widespread biological properties, such as anti-tumor, anti-microbial, and anti-HIV activities, enable *Stelletta*-derived MNPs to possess a broad application space and a bright market foreground in exploiting novel marine drug leads. In this review, we described the discovery of these metabolites and highlighted on the further synthesis and potential applications in future medicinal research of the most promising compounds. The research group of Prof. Yue-wei Guo (GUO LAB) has been engaged in the chemical and biological study of marine invertebrates, including *Stelletta* sponges, from Chinese Sea over 20 years, and this review paper is dedicated to Prof. Yue-wei Guo on the occasion of his 60th birthday, for his pioneer work on Chinese marine natural product chemistry.

Xuwen Li