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

Reviews

Acta Pharmaceutica Sinica B, 9 (2019) 871

Targeting the untargetable KRAS in cancer therapy

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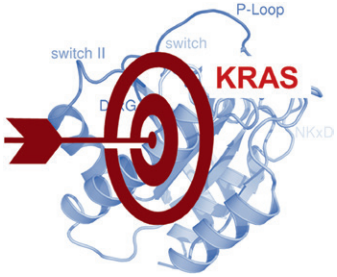

Continuous efforts in the past three decades failed to develop approved therapies for *KRAS* mutant cancer. Encouragingly, recent progress in the development of KRAS inhibitors either directly towards mutant KRAS or against the crucial steps required for KRAS activation may bring breakthrough for this long-pursued undruggable target.

Acta Pharmaceutica Sinica B, 9 (2019) 880

Structural simplification: an efficient strategy in lead optimization

Shengzheng Wang[a,b], Guoqiang Dong[a], Chunquan Sheng[a]

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Structural simplification is a powerful strategy for improving the efficiency and success rate of drug design. For large or complex lead compounds, structural simplification is helpful to discover drug-like molecules with improved synthetic accessibility and favorable pharmacodynamic/pharmacokinetic profiles.

Acta Pharmaceutica Sinica B, 9 (2019) 902

Multifunctional oral delivery systems for enhanced bioavailability of therapeutic peptides/proteins

Ying Han[a], Zhonggao Gao[a], Liqing Chen[a], Lin Kang[a], Wei Huang[a], Mingji Jin[a], Qiming Wang[a], You Han Bae[b]

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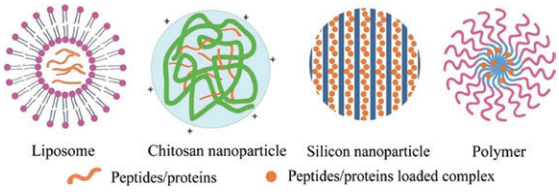

This review summarized various multifunctional delivery systems, including lipid-based particles, polysaccharide-based particles, inorganic particles, and synthetic multifunctional particles that achieved effective oral delivery of therapeutic peptides/proteins.

Original articles

Acta Pharmaceutica Sinica B, 9 (2019) 923

Inactivation of TFEB and NF-κB by marchantin M alleviates the chemotherapy-driven pro-tumorigenic senescent secretion

Huanmin Niu[a], Lilin Qian[a], Bin Sun[b], Wenjian Liu[a], Fang Wang[a], Qian Wang[a], Xiaotian Ji[a], Yanhai Luo[a], Effat Un Nesa[c], Hongxiang Lou[b], Huiqing Yuan[a]

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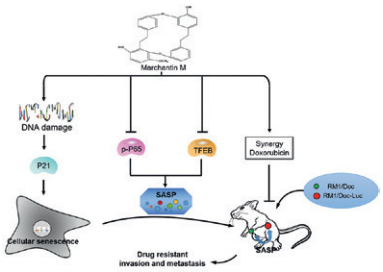

A naturally-occurring bisbibenzyl of marchantin M (Mar-M) can induce cellular senescence and transcriptionally suppress the senescence-associated secretary phenotype (SASP) through inactivation of TFEB and NF-κB in drug-resistant cells instead of normal fibroblast cells at low dose. Mar-M can alleviate the chemotherapy-driven pro-tumorigenic senescent secretion, leading to tumor regressions and prolonged survival with no detectable toxicity in drug-resistant mouse models. Mar-M synergistically cooperated with doxorubicin to remarkably lower its toxicity and enhance the antitumor efficacy.

Acta Pharmaceutica Sinica B, 9 (2019) 937

Synergistic antitumor activity of artesunate and HDAC inhibitors through elevating heme synthesis *via* synergistic upregulation of ALAS1 expression

Cai-Ping Chen, Kun Chen, Zhiqi Feng, Xiaoan Wen, Hongbin Sun

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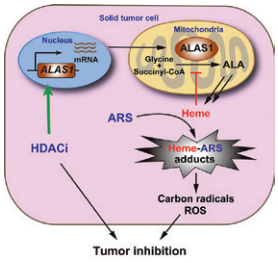

HDAC inhibitors (HDACi) cooperate with artesunate (ARS) to synergistically induce tumor cell death through promoting ALAS1 expression and subsequent heme synthesis, leading to enhanced cytotoxicity of ARS. This finding demonstrates a promising therapeutic approach to solid tumors based on modulating heme synthesis by the combination of artemisinin derivatives with HDACi.

Acta Pharmaceutica Sinica B, 9 (2019) 952

Direct interaction of DNMT inhibitors to PrP^C suppresses pathogenic process of prion

Dae-Hwan Kim[a,b], Chunyan Ren[c], Chongsuk Ryou[a,d], Jiaojie Li[e]

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[d]*Department of Pharmacy, Hanyang University, Ansan 15588, Republic of Korea*
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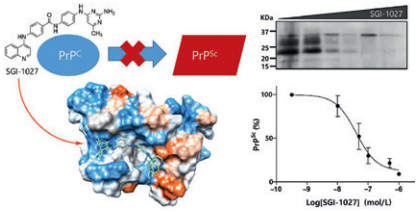

A novel activity of DNMT inhibitor SGI-1027 was discovered to suppress the pathogenic process of prion. The direct binding of SGI-1027 to prion protein with a normal conformation suppressed the formation of misfolded prion proteins.

Acta Pharmaceutica Sinica B, 9 (2019) 960

Improvement in affinity and thermostability of a fully human antibody against interleukin-17A by yeast-display technology and CDR grafting

Wei Sun, Zhaona Yang, Heng Lin, Ming Liu, Chenxi Zhao, Xueying Hou, Zhuowei Hu, Bing Cui

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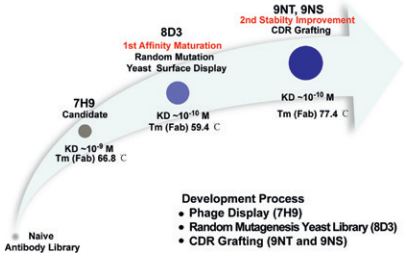


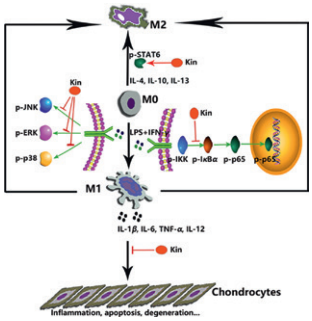
Anti-IL-17A antibodies were initially developed from a naïve fully human antibody library. The candidate was further affinity-matured by constructing a library of yeast-displayed single-chain Fv (scFv) mutants and thermostability-improved by CDR grafting. The lead anti-IL-17A mAb 9NT/S might be used as a potential best-in-class candidate for treating IL-17A related diseases.

Acta Pharmaceutica Sinica B, 9 (2019) 973

Kinsenoside attenuates osteoarthritis by repolarizing macrophages through inactivating NF-κB/MAPK signaling and protecting chondrocytes

Feng Zhou, Jingtian Mei, Xiuguo Han, Hanjun Li, Shengbing Yang, Minqi Wang, Linyang Chu, Han Qiao, Tingting Tang

Shanghai Key Laboratory of Orthopaedic Implants, Department of Orthopaedic Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China



Kinsenoside (Kin) repolarizes M1 macrophages to the M2 phenotype by inhibiting the phosphorylation of IκBα and further reducing downstream phosphorylation of P65. Moreover, Kin inhibits p-JNK, p-Erk and p-P38 in MAPK signaling pathway, and promotes p-STATA6, which is an important transcription factor for M2 macrophages polarization.

Acta Pharmaceutica Sinica B, 9 (2019) 986

Cilastatin protects against imipenem-induced nephrotoxicity *via* inhibition of renal organic anion transporters (OATs)

Xiaokui Huo[a,b,c], Qiang Meng[a,b,c], Changyuan Wang[a,b,c], Yanna Zhu[a], Zhihao Liu[a], Xiaodong Ma[a], Xiaochi Ma[a,b,c], Jinyong Peng[a,b,c], Huijun Sun[a,b,c], Kexin Liu[a,b,c]

[a]*Department of Clinical Pharmacology, College of Pharmacy, Dalian Medical University, Dalian 116044, China*
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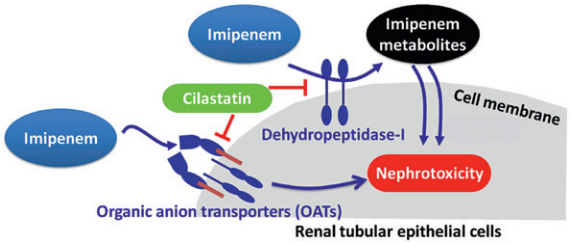

Renal OATs, for the first time, were identified to facilitate the transport and nephrotoxicity of imipenem, which could be abolished by cilastatin partly through OATs inhibition.

Acta Pharmaceutica Sinica B, 9 (2019) 997

Orthogonal assays for the identification of inhibitors of the single-stranded nucleic acid binding protein YB-1

Alexander J. Trevarton[a], Yan Zhou[b], Dehua Yang[b], Gordon W. Rewcastle[c,d], Jack U. Flanagan[c,d], Antony Braithwaite[e,f], Peter R. Shepherd[a,d], Cristin G. Print[a,d], Ming-Wei Wang[b,g], Annette Lasham[a,d]

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[c]*Auckland Cancer Society Research Centre, Auckland, New Zealand*
[d]*Maurice Wilkins Centre for Molecular Biodiscovery, University of Auckland, Auckland, New Zealand*
[e]*Department of Pathology, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand*
[f]*Maurice Wilkins Centre for Molecular Biodiscovery, University of Otago, Dunedin, New Zealand*
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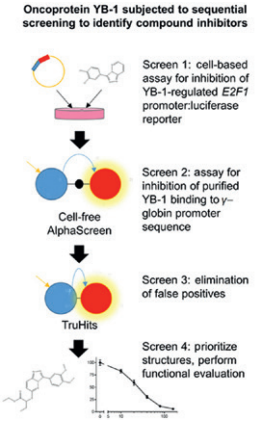

Novel AlphaScreen and luciferase reporter gene assays for the discovery of novel small-molecule inhibitors of the transcription factor YB-1 were developed and applied in a collection of 7360 compounds. Finally, three putative YB-1 inhibitors were yielded.

Acta Pharmaceutica Sinica B, 9 (2019) 1008

Upregulation of miR-489-3p and miR-630 inhibits oxaliplatin uptake in renal cell carcinoma by targeting OCT2

Lu Chen[a], Le Chen[a], Zhiyuan Qin[a], Jinxiu Lei[a], Sheng Ye[b], Kui Zeng[a], Hua Wang[c], Meidan Ying[a], Jianqing Gao[a], Su Zeng[a], Lushan Yu[a]

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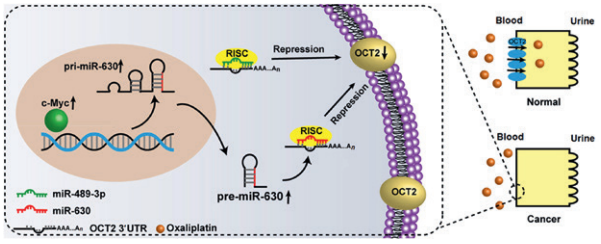
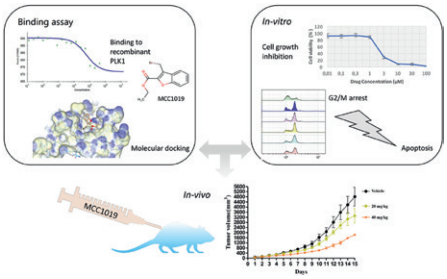


MiR-489-3p, c-Myc and miR-630 mediate OCT2 downregulation in RCC cells. MiR-489-3p and miR-630 is abnormally upregulated in RCC samples and exosomes, suppressing OCT2 expression by directly binding to the OCT2 3′-UTR. The increased binding of c-Myc to the promoter of pri-miR-630, contributes to the upregulation of miR-630 in RCC.

Acta Pharmaceutica Sinica B, 9 (2019) 1021

MCC1019, a selective inhibitor of the Polo-box domain of Polo-like kinase 1 as novel, potent anticancer candidate



Sara Abdelfatah[a], Angela Berg[b], Qi Huang[c], Li Jun Yang[c], Sami Hamdoun[a], Anette Klinger[d], Henry J. Greten[e], Edmond Fleischer[d], Thorsten Berg[b], Vincent K.W. Wong[c], Thomas Efferth[a]

[a]*Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz 55128, Germany*
[b]*Leipzig University, Institute of Organic Chemistry, Leipzig 04103, Germany*
[c]*State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Macau, China*
[d]*MicroCombiChem GmbH, Wiesbaden 65203, Germany*
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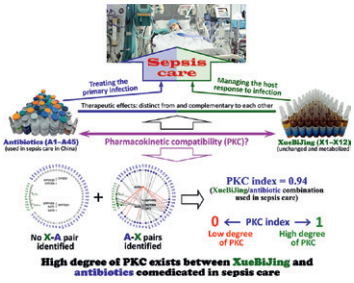
MCC1019 is a novel anticancer candidate that selectively targets PLK1. It mediates G2/M cell cycle arrest and cell death through induction of apoptosis and necroptosis. Inhibition of PLK1 downstream effectors like spindle assembly check points and cell growth pathway was well characterized. *In vivo* models revealed inhibition of tumor growth and metastasis.

Acta Pharmaceutica Sinica B, 9 (2019) 1035

High degree of pharmacokinetic compatibility exists between the five-herb medicine XueBiJing and antibiotics comedicated in sepsis care



Jian Li[a,b], Olajide E. Olaleye[a], Xuan Yu[a,b], Weiwei Jia[a], Junling Yang[a], Chuang Lu[c], Songqiao Liu[d], Jingjing Yu[e], Xiaona Duan[a], Yaya Wang[a], Kai Dong[f], Rongrong He[a], Chen Cheng[a], Chuan Li[a,b]

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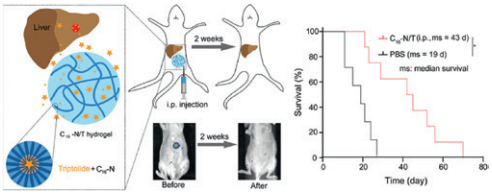
Managing the dysregulated host response to infection remains a major challenge in sepsis care. Chinese treatment guideline recommends adding XueBiJing, an intravenous five-herb injection, to antibiotic-based sepsis care. XueBiJing/antibiotic combination exhibited a high degree of pharmacokinetic compatibility at clinically relevant doses; this supports their concurrent use in sepsis care.

Acta Pharmaceutica Sinica B, 9 (2019) 1050

Injectable peptide hydrogel as intraperitoneal triptolide depot for the treatment of orthotopic hepatocellular carcinoma



Xiyue Zhao[a,b], Xiaoyu Liu[b], Pengcheng Zhang[b,c,e], Yiran Liu[b,f], Wei Ran[b,e], Ying Cai[b,e], Junyang Wang[b,g], Yihui Zhai[b,e], Guanru Wang[b], Yaping Ding[a], Yaping Li[b,d,e]

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C_{16}-N hydrogel containing triptolide was created as an intraperitoneal depot for the treatment of orthotopic hepatocellular carcinoma. After intraperitoneal injection, the hydrogel retained in the peritoneal cavity for more than 2 weeks with preferential drug accumulation in the liver, and doubled the median survival time of tumor-bearing mice without noticeable side effects to major organs.

Short Communication

Policy Forum

Acta Pharmaceutica Sinica B, 9 (2019)

Cover story

Front

An autophagy inducer rapamycin (RAP) was successfully incorporated into 7pep-modified polymer micelles (7pep-M-RAP). 7pep-M-RAP specifically targeted MCF-7 human breast cancer cells *via* transferrin receptor-mediated mechanism. It could efficiently prime mitochondria-associated autophagic cell death (ACD) and apoptosis when used in combination with cytotoxic paclitaxel-loaded micelles in the context of suitable administration schedule and sequence. This study suggests that the combined chemotherapy of targeting ACD may provide a rational strategy to improve therapeutic outcome of breast cancer, and simultaneous induction of ACD and apoptosis may be a promising anticancer modality.

Xiaoling Wang, Qiang Zhang

Back

Combination therapy using two or more therapeutic agents is progressively emerging as a cornerstone of cancer therapy. This article reveals that combination of artesunate (ARS) and HDAC inhibitor (HDACi) exerts synergistic tumor inhibition by inducing cell death. This process is similar to the cooperation of swab and detergent to remove stains. Swab and detergent represent ARS and HDACi, respectively. Single use of swab or detergent cannot decontaminate completely, whereas when used together, they efficiently remove stains through elevating detergent foam generation. Intriguingly, only in the presence of ARS, HDACi sustainably induces ALAS1 expression and subsequent heme synthesis. Heme is just like the detergent foam, mediating the cytotoxicity of ARS. This study not only reveals the mechanism of synergistic antitumor action of ARS and HDACi, but also indicates that modulation of heme synthesis pathway by the combination based on ARTs and other heme synthesis modulators represents a promising therapeutic approach to solid tumors.

Hongbin Sun