Acta Pharmaceutica Sinica B 2019;9(3):iii–viii

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–viii

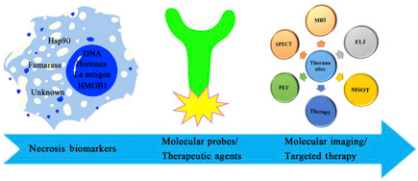
Reviews

Acta Pharmaceutica Sinica B, 9 (2019) 455

Updated developments on molecular imaging and therapeutic strategies directed against necrosis

Dongjian Zhang[a,b], Meng Gao[a,b], Qiaomei Jin[a,b], Yicheng Ni[a,b,c], Jian Zhang[a,b]

[a]*Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing 210028, China*
[b]*Laboratories of Translational Medicine, Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing 210028, China*
[c]*Theragnostic Laboratory, Campus Gasthuisberg, KU Leuven, Leuven 3000, Belgium*



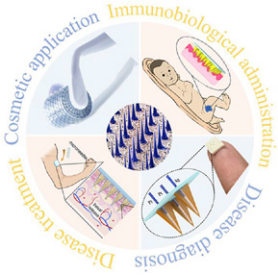
This review describes the updated joint efforts to develop necrosis imaging probes and therapeutic strategies through targeting the biomarkers exposed by necrotic cells as well as discusses current challenges and possible future research directions.

Acta Pharmaceutica Sinica B, 9 (2019) 469

Recent advances of microneedles for biomedical applications: drug delivery and beyond

Jian Yang[a], Xinli Liu[b], Yunzhi Fu[a], Yujun Song[b]

[a]*College of Materials Science and Chemical Engineering, Hainan University, Haikou 570228, China*
[b]*College of Engineering and Applied Sciences, Nanjing University, Nanjing 210093, China*



This review describes the updated joint efforts to develop necrosis imaging probes and therapeutic strategies through targeting the biomarkers exposed by necrotic cells as well as discusses current challenges and possible future research directions.

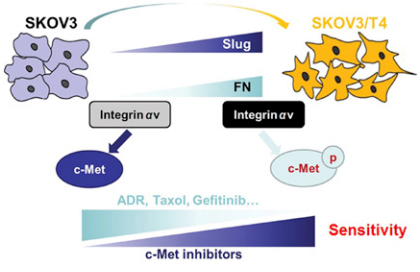
Original articles

Acta Pharmaceutica Sinica B, 9 (2019) 484

Targeting slug-mediated non-canonical activation of c-Met to overcome chemo-resistance in metastatic ovarian cancer cells

Linlin Chang[a], Yan Hu[a], Yingying Fu[a], Tianyi Zhou[a], Jun You[b], Jiamin Du[a], Lin Zheng[a], Ji Cao[a], Meidan Ying[a], Xiaoyang Dai[a], Dan Su[b], Qiaojun He[a], Hong Zhu[a], Bo Yang[a]

[a]*Zhejiang Province Key Laboratory of Anti-Cancer Drug Research, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China*
[b]*Zhejiang Cancer Hospital, Hangzhou 310022, China*



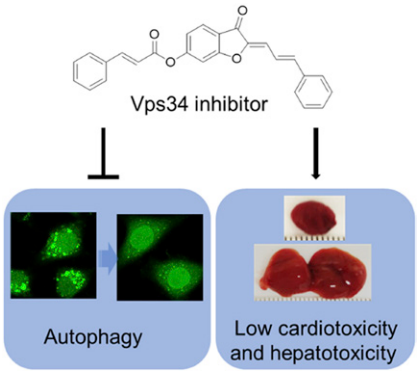
In order to overcome chemotherapy resistance in metastatic ovarian cancer patients, we enriched a metastatic subpopulation of SKOV3 cells to explore the mechanisms underlying metastatic-associated drug resistance. Quantitative genomic and functional analyses uncover the critical roles of slug in metastatic-associated drug resistance, which can be overcome by c-Met inhibitor(s) both *in vitro* and *in vivo*. The finding also presents a new exciting opportunity to overcome metastatic-associated drug resistance for ovarian cancer patients by targeting c-Met signaling, particularly those patients harboring high expression levels of slug and poor prognosis.

Acta Pharmaceutica Sinica B, 9 (2019) 537

Aurone derivatives as Vps34 inhibitors that modulate autophagy

Guodong Li[a], Joshua William Boyle[b], Chung-Nga Ko[c], Wu Zeng[d], Vincent Kam Wai Wong[d], Jian-Bo Wan[a], Philip Wai Hong Chan[b,e], Dik-Lung Ma[c], Chung-Hang Leung[a]

[a]*State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau 999078, China*
[b]*School of Chemistry, Monash University, Clayton 3800, Australia*
[c]*Department of Chemistry, Hong Kong Baptist University, Hong Kong 999077, China*
[d]*State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Macau 999078, China*
[e]*Department of Chemistry, University of Warwick, Coventry CV4 7AL, UK*



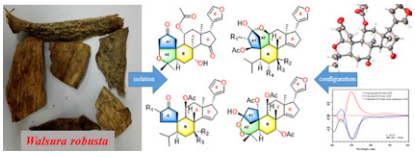
We identified aurone derivative **1a** as an ATP-competitive inhibitor of Vps34 inhibitor. **1a** prevented autophagy in human cells induced either by starvation or by an mTOR inhibitor. *In vivo* examination showed that **1a** was able to promote p62 accumulation without affecting the morphology of mice heart and liver.

Acta Pharmaceutica Sinica B, 9 (2019) 545

Bioactive A-ring rearranged limonoids from the root barks of *Walsura robusta*

Faliang An, Xiaobing Wang, Minghua Yang, Jun Luo, Lingyi Kong

Jiangsu Key Laboratory of Bioactive Natural Product Research and State Key Laboratory of Natural Medicines, Department of Natural Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China



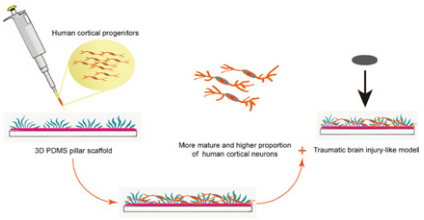
Twenty A/B spiro-type limonoids (**1**–**20**) including seven new neotecleanin-type limonoids (**1**–**7**), seven novel limonoids (**8**–**14**) with 5-oxatricyclo[5.4.0.$1^{1,4}$]hendecane ring system, and two key precursors (**15**–**16**) were isolated from the root barks of *Walsura robusta*. Walrobsin M (**11**) significantly inhibited inflammatory activity with IC_{50} value of 7.96 μmol/L, and down-regulated phosphorylation levels of ERK and p38 in a dose-dependent manner.

Acta Pharmaceutica Sinica B, 9 (2019) 557

Develop a 3D neurological disease model of human cortical glutamatergic neurons using micropillar-based scaffolds

Cheng Chen[a,b,c], Xin Dong[a,b], Kai-Heng Fang[a,b], Fang Yuan[a,b], Yao Hu[a,b], Min Xu[a,b], Yu Huang[c], Xixiang Zhang[d], Danjun Fang[b], Yan Liu[a,b,e]

[a]*Institute for Stem Cell and Neural Regeneration, School of Pharmacy, Nanjing Medical University, Nanjing 211166, China*
[b]*Key Laboratory of Targeted Intervention of Cardiovascular Disease, Collaborative Innovation Center for Cardiovascular Disease Translational Medicine, School of Pharmacy, Nanjing Medical University, Nanjing 211166, China*
[c]*Department of Biological Engineering, Utah State University, Logan, UT 84322, USA*
[d]*Physical Sciences and Engineering Division (PSE), King Abdullah University of Science and Technology, Thuwal 23955-6900, Kingdom of Saudi Arabia*
[e]*Institute for Stem Cell and Regeneration, Chinese Academy of Sciences, Beijing 100101, China*



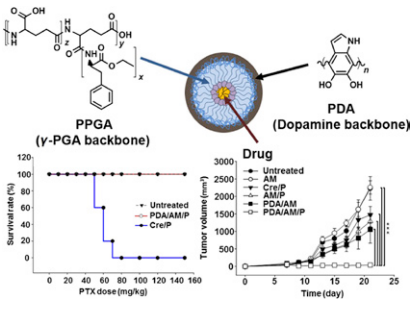
Based on a polydimethylsiloxane (PDMS) pillar-based 3D scaffold, more mature and higher proportion of human cortical neurons was achieved. This study provided an *in vitro* disease-like model of traumatic brain injury, which would facilitate mechanistic studies and drug screening for neurotrauma or other neurological diseases.

Acta Pharmaceutica Sinica B, 9 (2019) 565

Safety and photochemotherapeutic application of poly(γ-glutamic acid)-based biopolymeric nanoparticle

Dongyoon Kim[a], Quoc-Viet Le[a], Young Bong Kim[b], Yu-Kyoung Oh[a]

[a]*College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 08826, Republic of Korea*
[b]*Department of Biomedical Engineering, Konkuk University, Seoul 05029, Republic of Korea*



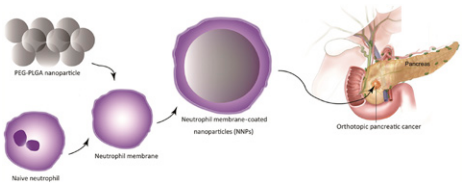
The safety of nanomaterials was enhanced using poly(γ-glutamic acid) and dopamine as building blocks. Amphiphilic phenylalanine derivative of poly(γ-glutamic acid) formed a core nanomaterials with hydrophobic paclitaxel inside. The polydopamine-coated and paclitaxel-loaded amphiphilic poly(γ-glutamic acid)-based nanoparticles exerted near-infrared-responsiveness and provided synergistic photothermal chemotherapeutic effect.

Acta Pharmaceutica Sinica B, 9 (2019) 575

Neutrophil-mimicking therapeutic nanoparticles for targeted chemotherapy of pancreatic carcinoma

Xi Cao, Ying Hu, Shi Luo, Yuejing Wang, Tao Gong, Xun Sun, Yao Fu, Zhirong Zhang

Key Laboratory of Drug Targeting and Drug Delivery Systems, Ministry of Education, West China School of Pharmacy, Sichuan University, Chengdu 610041, China



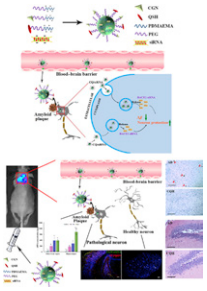
Neutrophil membrane-coated nanoparticles (NNPs) have been developed to overcome the blood–pancreas barrier to achieve site-specific drug delivery.

Acta Pharmaceutica Sinica B, 9 (2019) 590

Small interfering RNA delivery to the neurons near the amyloid plaques for improved treatment of Alzheimer's disease

Qian Guo, Xiaoyao Zheng, Peng Yang, Xiaoying Pang, Kang Qian, Pengzhen Wang, Shuting Xu, Dongyu Sheng, Liuchang Wang, Jinxu Cao, Wei Lu, Qizhi Zhang, Xinguo Jiang

Key Laboratory of Smart Drug Delivery, Ministry of Education, & State Key Laboratory of Molecular Engineering of Polymers, School of Pharmacy, Fudan University, Shanghai 201203, China



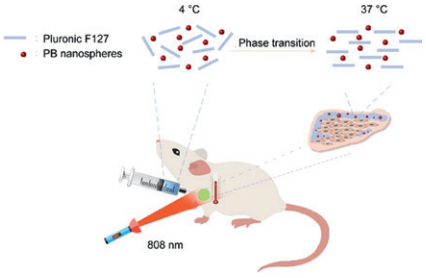
In this study, the nanocomplexes were prepared with an siRNA against β-site amyloid precursor protein-cleaving enzyme 1 (BACE1), the rate-limiting enzyme of Aβ production, as the therapeutic siRNA of Alzheimer's disease.

Acta Pharmaceutica Sinica B, 9 (2019) 604

Prussian blue nanosphere-embedded *in situ* hydrogel for photothermal therapy by peritumoral administration

Jijun Fu[a,b], Bo Wu[a,c], Minyan Wei[b], Yugang Huang[a,b], Yi Zhou[a,b], Qiang Zhang[b], Lingran Du[b]

[a]*The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou 510700, China*
[b]*Key Laboratory of Molecular Target & Clinical Pharmacology, School of Pharmaceutical Sciences, Guangzhou Medical University, Guangzhou 511436, China*
[c]*Center of Pharmaceutical Research and Development, School of Pharmaceutical Sciences, Guangzhou Medical University, Guangzhou 511436, China*



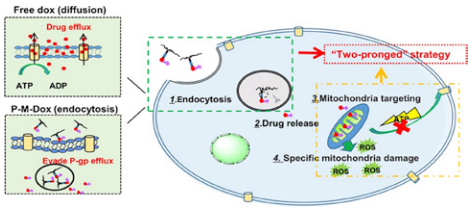
This study developed an *in situ* hydrogel containing Prussian blue (PB) nanospheres to treat breast cancer. The injectable hydrogel shows an excellent tumor curing effect and biocompatibility. The PB nanospheres were eliminated through the urine.

Acta Pharmaceutica Sinica B, 9 (2019) 615

Overcoming chemotherapy resistance *via* simultaneous drug-efflux circumvention and mitochondrial targeting

Minglu Zhou[a], Lijia Li[a], Lian Li[b], Xi Lin[a], Fengling Wang[a], Qiuyi Li[a], Yuan Huang[a]

[a]*Key Laboratory of Drug Targeting and Drug Delivery System (Ministry of Education), West China School of Pharmacy, Sichuan University, Chengdu 610041, China*
[b]*Department of Pharmaceutics and Pharmaceutical Chemistry/Center for Controlled Chemical Delivery, University of Utah, Salt Lake City, UT 84112, USA*



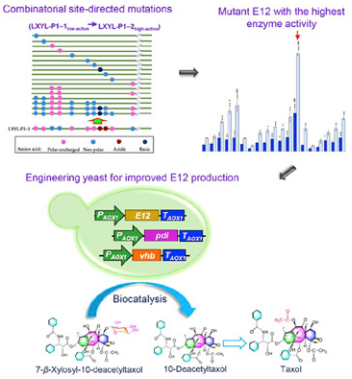
Free Dox that enters cells by diffusion was vulnerable to P-gp efflux. On the contrary, P-M-Dox that enters cells by endocytosis can effectively evade P-gp efflux pump on the cell membrane. Then, P-M-Dox responsively releases MPP modified doxorubicin (M-Dox) in the lysosomal acidic environment, and eventually achieves excellent mitochondria targeting for elevating reactive oxygen species generation and minimizing ATP production, thereby killing drug-resistant tumor cells through simultaneous drug efflux circumvention and direct mitochondria delivery.

Acta Pharmaceutica Sinica B, 9 (2019) 626

Combinatorial mutation on the β-glycosidase specific to 7-β-xylosyltaxanes and increasing the mutated enzyme production by engineering the recombinant yeast

Jing-Jing Chen, Xiao Liang, Fen Wang, Yan-Hua Wen, Tian-Jiao Chen, Wan-Cang Liu, Ting Gong, Jin-Ling Yang, Ping Zhu

State Key Laboratory of Bioactive Substance and Function of Natural Medicines & NHC Key Laboratory of Biosynthesis of Natural Products, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, China



The combinatorial mutation strategy was employed to increase the β-glycosidase activity, and the mutant E12 with the highest enzyme activity was obtained. The E12 production in the yeast was further improved by co-expressing the molecular chaperone PDI (protein disulfide isomerase) and the *Vitreoscilla* hemoglobin under the promoter P_{AOX1}. This engineered yeast can be used for the biocatalysis of 7-β-xylosyl-10-deacetyltaxol to 10-deacetyltaxol for Taxol semi-synthesis.

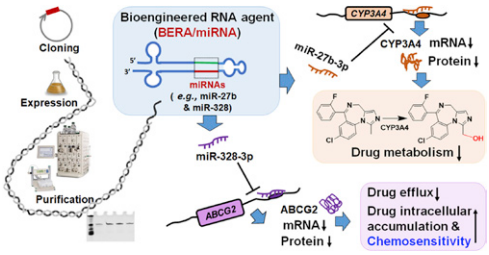
Short communication

Acta Pharmaceutica Sinica B, 9 (2019) 639

Bioengineered miR-27b-3p and miR-328-3p modulate drug metabolism and disposition *via* the regulation of target ADME gene expression

Xin Li[a,c], Ye Tian[b,c], Mei-Juan Tu[c], Pui Yan Ho[c], Neelu Batra[c], Ai-Ming Yu[c]

[a]*Key Laboratory of Molecular Target & Clinical Pharmacology, School of Pharmaceutical Sciences & the Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou 511436, China*
[b]*Lab for Bone Metabolism, Key Lab for Space Biosciences and Biotechnology, School of Life Sciences, Northwestern Polytechnical University, Xi'an 710072, China*
[c]*Department of Biochemistry & Molecular Medicine, UC Davis School of Medicine, Sacramento, CA 95817, USA*



A novel RNA biotechnology was used to produce bioengineered miRNA agents (BERA), namely BERA/miR-27b-3p and BERA/miR-328-3p, which were selectively processed to target miR-27-3p and -328-3p to modulate the expression of CYP3A4 enzyme and ABCG2 transporter, respectively, in human cells, and subsequently alter cellular drug metabolism and disposition capacity.

Regulation and guideline

Acta Pharmaceutica Sinica B, 9 (2019) 648

Guidance for the clinical evaluation of traditional Chinese medicine-induced liver injury

Xiaohe Xiao[a], Jianyuan Tang[b], Yimin Mao[c], Xiuhui Li[d], Jiabo Wang[a], Chenghai Liu[e], Kewei Sun[f], Yong'an Ye[g], Zhengsheng Zou[h], Cheng Peng[i], Ling Yang[j], Yuming Guo[a], Zhaofang Bai[a], Tingting He[a], Jing Jing[a], Fengyi Li[k], Na An[b]

[a]*China Military Institute of Chinese Medicine, Beijing 302 Hospital of China, Beijing 100039, China*
[b]*Center for Drug Evaluation, China Food and Drug Administration, Beijing 100022, China*
[c]*Renji Hospital of Shanghai Jiaotong University, Shanghai 200127, China*
[d]*Beijing Youan Hospital of Capital Medical University, Beijing 100069, China*
[e]*Shuguang Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai 200127, China*
[f]*First Affiliated Hospital of Hunan University of Traditional Chinese Medicine, Changsha 410007, China*
[g]*Dongzhimen Hospital of Beijing University of Traditional Chinese Medicine, Beijing 100700, China*
[h]*Center for Non-infectious Liver Diseases, Beijing 302 Hospital of China, Beijing 100039, China*
[i]*College of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China*
[j]*College of Pharmacy, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China*
[k]*Center for Infectious Liver Diseases, Beijing 302 Hospital of China, Beijing 100039, China*

Acta Pharmaceutica Sinica B, 9 (2019)

Cover story

Front

In the tug-of-war between human and cancer, the latter usually gains the upper hand, especially when it comes to the metastatic ovarian cancer which is highly resistant to chemotherapy. This is similar with the Chinese historical event back in the Southern Song Dynasty. At that time, almost no one could stop invasion of the cataphract from Jin Dynasty, since the war-horses from Jin were fully armed with impenetrable armour, as shown in the cover image. Fortunately, a general of Song Dynasty, Yue Fei, developed a kind of spear with hooked sickle, which could particularly cut off the legs of those armed war-horses, thus bring down these "undefeatable" Jin enemies. Yue's army initiated effective counterattack against Jin's cataphract, defeating one enemy after another. This well-known patriot has been the national folk hero in China since then. Our recent study uncovers that slug, a transcription factor essential for metastasis, contributes to the drug resistance of ovarian cancer cells. Intriguingly, slug activates c-Met in a ligand-independent manner, thus opening a window for c-Met inhibitors (*e.g*., XL184) to specifically targeting these resistant cells. Thus c-Met inhibitors are just like Yue's army, efficiently killing those highly resistant metastatic ovarian cancer cells, even though they are "fully armed" with hyperactivated slug. This study not only uncovers the critical roles of slug in drug resistance of ovarian cancer, but also highlights a promising therapeutic strategy by targeting the noncanonical activation of c-Met in slug-positive ovarian cancer patients with poor prognosis.

Hong Zhu, Bo Yang

Back

The discovery and structure elucidation of limonoids, which possess complex structures and/or potent bioactivities, but only in small quantities, are exceptionally difficult in traditional folk medicinal plants in the Meliaceae plant families. This article describes how to use modern analytical instruments, such as NMR, HPLC and HR-MS, just like omnipotent cartoon character in the famous Chinese animation "Calabash Brothers" with "clairvoyant" and "clairaudience", to find the minor, complex, and bioactive limonoids from the root bark of traditional folk medicine *Walsura robusta*. The isolation and identification were applied based on the characteristic ultraviolet absorption, molecular weight range and resonance fingerprints of target limonoids. Systematic study of the root barks of *Walsura robusta* led to 16 novel A-ring rearranged limonoids, along with 4 known analogues based on our clairvoyance ability—HPLC, HR-MS and NMR. Partial isolates showed modest anti-inflammatory activities, especially walrobsin M, which down-regulated phosphorylation levels of ERK and p38 in *Propionibacterium acnes*-stimulated THP-1 human monocytic cells in a dose-dependent manner. This study aims to provide a pathway to discover novel bioactive natural drug leads in traditional folk medicinal plants.

Jun Luo, Lingyi Kong