

Combined CDK overcomes MEK inhibitors resistance in Plexiform Neurofibroma of neurofibromatosis type 1

Zhichao Wang and Qingfeng Li

Shanghai Ninth People's Hospital, China

MAPK/extracellular signal-regulated kinase kinase (MEK) 1/2 inhibitors (MEKis) have recently achieved surprising success in treating unresectable Plexiform Neuro Fibromas (PNFs). However, few studies have investigated the mechanisms of MEKi resistance in patients with PNF. We determined the efficacy of six different MEKis for treating PNFs, explored drug resistance mechanisms, and identified potential combination therapies to overcome resistance. By screening drug efficacy among six MEKis in human NF1-deficient PNF cell lines, TAK-733 was found to reduce PNF cell viability the most. We then cultured the TAK-733-resistant cells and explored the potential targets for further treatment. Both high-throughput drug screening and RNA sequencing analyses of MEKi-resistant PNF cells identified cyclin-dependent kinase inhibitors as potential agents for PNFs. Dinaciclib, a cyclin-dependent kinase inhibitor, showed synergistic effects on MEKi-resistant cells. Coadministration of dinaciclib and TAK-733 significantly reduced cell viability and inhibited sphere formation and colony formation. Dinaciclib did not affect MEK signaling but decreased the expression of several prosurvival proteins, including survivin and cyclin-dependent kinase 1, to induce apoptosis and inhibit mitosis. TAK-733/dinaciclib combination therapy induced tumor reduction in PNF patient-derived xenografts mouse models. Therefore, the combination of MEKi and cyclin-dependent kinase inhibitor may be promising for treating inoperable PNFs, especially when drug resistance exists. Our findings provide evidence for future clinical trials with MEKi resistant patients with PNF.

Recent Publications

1. Wei Wang^{1,#}, Xi-Wei Cui^{1,#}, Yi-Hui Gu^{1,#}, Cheng-Jiang Wei¹, Yue-Hua Li¹, Jie-Yi Ren¹, Man-hon Chung¹, Re-han-gu-li Aimaier¹, Hai-Bing Zhang², Qing-Feng Li^{1,*}, Zhi-Chao Wang^{1,*}. Combined Cyclin-Dependent Kinase Inhibition Overcomes MAPK/Extracellular Signal-Regulated Kinase Kinase Inhibitor Resistance in Plexiform Neurofibroma of Neurofibromatosis Type I. *Journal of Investigative Dermatology*. 2021. 142(3 Pt A):613-623. IF:8.552:Q1 JCR
2. Wei Wang^{1, #}, MD; Cheng-Jiang Wei^{1, #}, MD; Xi-Wei Cui^{1, #}, MD; Jie-Yi Ren¹, MD; Yi-Hui Gu¹, MD; Bin Gu¹, MD; Qing-Feng Li^{1, *}, MD, PhD; Zhi-Chao Wang^{1, *}, MD, MPH. Impacts of NF1 gene mutations and genetic modifiers in neurofibromatosis type 1. *Frontiers in Neurology*. 2021. 12:704639. IF:4.001: Q2 JCR
3. Jieyi Ren[#], Yihui Gu[#], Xi-Wei Cui[#], Manmei Long[#], Wei Wang, Chengjiang Wei, Bin Gu, Haibing Zhang, Qingfeng Li^{*}, Zhichao Wang^{*}. Protein Tyrosine Phosphatase Receptor S Acts as a Metastatic

35th World Pediatrics Conference

August 01-02, 2022

WEBINAR

Suppressor in Malignant Peripheral Nerve Sheath Tumor via Profilin 1-Induced Epithelial-Mesenchymal Transition. *Frontiers in Cell and Developmental Biology*. 2020 Oct 9;8:582220 IF6.684:Q2 JCR

4. Cheng-Jiang Wei#, Yi-Hui Gu#, Wei Wang#, Jie-Yi Ren, Xi-Wei Cui, Xiang Lian, Jin Liu, Hui-Jing Wang, Bin Gu, Qing-Feng Li^{1*}, Zhi-Chao Wang*, A review of the role of fibroblasts in the growth and development of neurogenic tumors. *Annals of Translational Medicine* 2020 Nov;8(21):1462. IF:3.932:Q3 JCR
5. Cheng-Jiang Wei#, Chen Yan#, Yan Tang#, Wei Wang, Yi-Hui Gu, Jie-Yi Ren, Xi-Wei Cui, Xiang Lian, Jin Liu, Hui-Jing Wang, Bin Gu, Tao Zan, Qing-Feng Li^{*}, Zhi-Chao Wang*. Computed Tomography-Based Differentiation of Benign and Malignant Craniofacial Lesions in Neurofibromatosis Type I Patients: A Machine Learning Approach. *Frontiers in Oncology*, 2020. 10:1192. IF:6.244:Q2 JCR

Biography

Zhichao Wang is associate chief surgeon and associate professor from Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. His clinical and research focused on comprehensive treatments of neurofibromatosis (including radical surgical resection, tumor reduction surgery, organ reconstruction after facial neurofibromatosis resection, neurofibromatosis related clinical trials). He is the winner of Shanghai Youth Top Talent, the winner of "Rising Star" of Shanghai Science and Technology Commission, the winner of "Chenguang Program" of Shanghai Education Commission and the Sailing Plan of Shanghai Science and Technology Commission Young Science and Technology Talents.

Zhichao Wang has several academic publications in famous journals including *Journal of Investigative Dermatology*, *JAMA Facial Plastic Surgery* as first or corresponding authors. The total impact factor reached above 150 points with more than 500 citations. He obtained 2 national invention patents. He led and participated in 6 national and provincial scientific research projects. He is also on the editorial board of *Annals of Translational Medicine* and *Translational Pediatrics*. He won the second prize of Shanghai Teachers teaching Innovation Competition and other 9 teaching awards.

Received: April 15, 2022; **Accepted:** April 18, 2022; **Published:** August 01, 2022
