

## 5<sup>th</sup> Asia-Pacific Summit on **Cancer Therapy**

July 20-22, 2015 Brisbane, Australia

### **Dual inhibition of Cdc7 and Cdk9 by PHA-767491 suppresses hepatocarcinoma synergistically with 5-fluorouracil**

**Xi Chen**  
Zhejiang University, China

Activation of checkpoint kinase 1 (Chk1) is essential in chemo resistance of hepatocarcinoma (HCC) to 5-fluorouracil (5-FU) and other anti metabolite family of drugs. In this study, we demonstrated that PHA-767491, a dual inhibitor of two cell cycle checkpoint kinases, cell division cycle kinase 7 (Cdc7) and cyclin-dependent kinase 9 (Cdk9) has synergistic antitumor effect with 5-FU to suppress human HCC cells both in vitro and in vivo. Compared with the sole use of each agent, PHA-767491 in combination with 5-FU exhibited much stronger cytotoxicity and induced significant apoptosis manifested by remarkably increased caspase 3 activation and poly (ADP-Ribose) polymerase (PARP) fragmentation in two HCC cell lines BEL-7402 and Huh7. PHA-767491 directly counteracted the 5-FU-induced phosphorylation of Chk1, a substrate of Cdc7 and decreased the expression of the anti-apoptotic protein myeloid leukemia cell 1 (Mcl1), a downstream target of Cdk9. In tumor tissues sectioned from nude mice HCC xenografts, administration of PHA-767491 also decreased Chk1 phosphorylation and increased in situ cell apoptosis. Our study suggests that PHA-767491 could enhance the efficacy of 5-FU by inhibiting Chk1 phosphorylation and down-regulating Mcl1 expression through inhibition of Cdc7 and Cdk9, thus combinational administration of PHA-767491 with 5-FU could be potentially beneficial to patients with advanced and resistant HCC.

#### **Biography**

Xi Chen got her MD degree from Peking University Health Science Center, China and later a PhD degree in Biochemistry from King's College London, UK. Her Postdoctoral training was received in the University of Pittsburgh, USA. She started working as an Associate Professor in Zhejiang University since 2011. She is also the Deputy Director of the central lab of the Children's Hospital, Zhejiang University School of Medicine. She has published 15 peer-reviewed papers in scientific journals and presented in several international conferences. Her current research interest focuses on the treatment of cancer.

[chchenxi@zju.edu.cn](mailto:chchenxi@zju.edu.cn)

#### **Notes:**