HMPL-523, a Novel SYK Inhibitor, Showed Anti-tumor Activities in Vitro and in Vivo

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Introduction

SYK, a Src homology 2 (SH2) and SH3 domain-containing kinase, is a critical regulator of BCR signaling. It plays a pivotal role in the regulation of B-cell receptor (BCR) signal pathways.

HMPL-523 is a novel, highly potent and selective SYK inhibitor. The preclinical anti-tumor activity of HMPL-523 was evaluated in this study.

Methods

A. HMPL-523 is a potent and selective SYK inhibitor

SYK IC50 (µM) 

HMPL-523 0.025 (1X) 0.054 (1X)

R406 0.063 (3.5X) 0.009 (0.3X)

GS9973 <70% inhibition at 3 µM

B. HMPL-523 inhibited cell survival and SYK signaling pathway in BA/F3 and REC-1 cells

C. HMPL-523 inhibited cell survival in a panel of human lymphoma and leukemia cell lines and induced apoptosis in REC-1 cells

Figure 1. BCR signaling pathway

Figure 2. Inhibition on p-BLNK activation in REC-1 and ARH-77 cells

Figure 3. Effect of HMPL-523 on cell survival (a) and SYK signaling pathway (b) in BA/F3 and REC-1 cells

Figure 4. The cells survival inhibition of HMPL-523, deluxid and deluxidins in lymphoma and leukemia cell lines

Figure 5. HMPL-523, R406 and GS9973 increased apoptotic rate in REC-1 cells

D. Combination of HMPL-523 with other drugs to promote cell killing in Diffuse large B-cell lymphoma (DLBCL) cells through inducing apoptosis

Figure 6. (a) HMPL-523 combined with other drugs to inhibit cell survival in DLBCL. (b) Co-treatment of HMPL-523 and PKI-5858 selective inhibitor caused apoptosis in SU-DHL-5 cells

E. SYK signaling inhibition and anti-tumor activity of HMPL-523 in vivo

Figure 7. (a) HMPL-523 dose-dependently increased the apoptotic rate in REC-1 tumors xenografts. (b) HMPL-523 dose-dependently increased the life span of mice bearing Ba/F3 TEL-SYK tumors. (c) HMPL-523 at 100 mg/kg inhibited tumor growth in REC-1 subcutaneous xenograft model.

Summary

HMPL-523 is a potent and highly selective SYK inhibitor.

The in vitro and in vivo anti-tumor activity of HMPL-523 is mediated by SYK signaling pathway inhibition.

The synergistic anti-tumor effect of combination of HMPL-523 with other targeted therapy or chemotherapy in DLBCL cell line warrants further investigation of combination therapy in clinical trials.

Reference

[1] Pharmacology & Therapeutics 144 (2014) 338–348

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