KDDF
Korea Drug Development Fund

Asset #13
Dana-Farber Cancer Institute

CDK8 and CDK19 Small Molecule Inhibitors and Degraders

Therapeutic Area	Immunology, Oncology	**Indications**	Solid tumors, Leukemias (AML, MDS), Autoimmune Diseases
Modality	Small Molecule	**Development Stage**	Hit to Lead/Lead Optimization

Overview

Background

- CDK8 and its paralog CDK19 are part of the Mediator complex that controls RNA polymerase II, the enzyme responsible for transcribing mRNA. Deregulation of CDK8 has been linked to many cancers including cancers of the breast, colon, leukemias, melanoma, pancreas, and prostate. Targeting CDK8/19 has been recognized and exploited for its potential as a cancer therapy as is shown by ongoing clinical trials focused on metastatic or advanced solid tumors, and blood cancers including AML and high-risk MDS. Furthermore, CDK8/19 inhibition may also offer treatment potential for patients with autoimmune disease. Preclinical studies have shown that CDK8/19 inhibition leads to an increase in regulatory T (Treg) cells protecting the body from an autoimmune response.
- Researchers at DFCI have developed a portfolio of CDK8/19 pyrazolopyridine and steroid-based small molecule inhibitors as well as ProTaC degraders derived thereof. The compositions show potent and selective effects on CDK8 and CDK19 activity by either inhibition or degradation, making them a trove of attractive new molecules for further development into promising new therapeutics to treat cancer or autoimmune diseases.

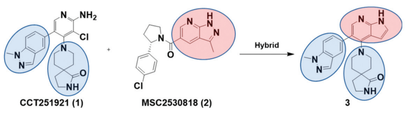
Technology Advantages

- Low single digit nM IC50 assay readouts predictive of high potency
- High CDK8/19 selectivity with negligible off-target binding as determined by broad kinome screening, predictive of low toxicity drug propertiesA potentially effective strategy for the treatment of lung cancer with KRAS mutation or mutant KRAS-driven lung cancer

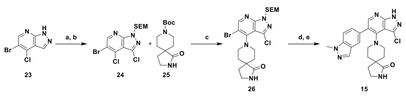
Key Data

A highly potent and selective inhibitor of CDK8/19 (JH-XVI-178) displays low clearance and moderate oral pharmacokinetic properties.

A



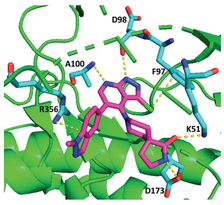
B



JH-XVI-178

(A) Hybridization design strategy leading to the development of this series of CDK8/19 inhibitors. (B) Preparation of JH-XVI-178, [Reagents and conditions: (a) NCS, CH3CN, 70 °C; (b) SEM-Cl, NaH, DMF; (c) NMP, TEA, 180 °C μW; (d) Pd(dppf)Cl2, tBuXPhos,1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- 1H-indazole, Na2CO3, 1,4-dioxane, H2O, 100 °C; (e) HCl, MeOH, 70 °C]

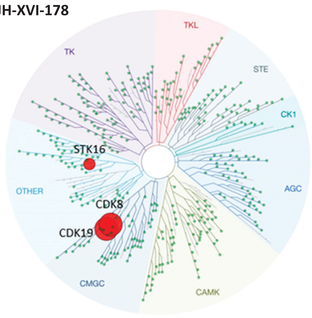
C



(C) Docking study of JH-XVI-178 using the cocrystal structure of 1 in complex with CDK8 (PDB ID 5HBJ). Dashed lines suggest important interactions

D

JH-XVI-178



In Vitro	
CDK8 IC_{50} (nM)	1
CDK19 IC_{50} (nM)	2
Cl_{int}a ($\mu L \cdot min^{-1} \cdot mg^{-1}$)	15
In Vivo Mouse PK[b]	
C_{Max}[c] (μM)	1.04
AUC_{last} (min × ng/mL)[c]	51863
$T_{1/2}$[c] (h)	1.3
Cl ($mL \cdot min^{-1} \cdot mg^{-1}$)	17
V_{ss} (L/kg)	0.8
F (%)	8

(D) KINOMEscan results for JH-XVI-178 at a concentration of 1 μM with a cutoff of 90% inhibition. (E) Pharmacokinetic profile, [[a] Mouse hepatocytes. [b] Formulation: 0.2 mg/mL (IV) and 1 mg/mL (PO) solution in 5/95 DMSO/30% Captisol; 2 mg/kg IV dose and 10 mg/kg PO dose. [c] Following PO dose.]

IP Status & Publication(s)

Intellectual Property

Patent Number
US 11247991 B2 (2022.02.15)
US 11285144 B2 (2022.03.29)

Patent Family
PCT, US, EP, JP, CN, CA, AU
PCT, US

Publication(s)

- Hatcher, J. M. et al. (2018). Development of highly potent and selective steroidal inhibitors and degraders of CDK8. ACS Medicinal Chemistry Letters, 9(6), 540–545.
- Hatcher, J. M. et al. (2021). Development of highly potent and selective pyrazolopyridine inhibitor of CDK8/19. ACS Medicinal Chemistry Letters, 12(11), 1689–1693.