4 ERK5 inhibitor as key regulator in cancer treatment

Asset Overview

Product Type	Small molecules
Indication	Cancer (breast and prostate) and other diseases
Current Stage	Lead optimization
Target(MoA)	ERK5 (also known as MAPK7 and BMK-1)
Brief Description	Here, we perform a targeted screen for kinase inhibitors, which modulate the naive-primed pluripotent transition. We find that XMD compounds, which selectively inhibit Erk5 kinase and BET bromodomain family proteins, drive ESCs toward primed pluripotency. Using compound selectivity engineering and CRISPR/Cas9 genome editing, we reveal distinct functions for Erk5 and Brd4 in pluripotency regulation. We show that Erk5 signaling maintains ESCs in the naive state and suppresses progression toward primed pluripotency and neuroectoderm differentiation.
Organization	Dana-Farber Cancer Institute

Differentiation

□ **Selective inhibitor validates ERK5 as key regulator of ESC identity**

- Beyond these and several other core pluripotency pathways, the role of protein kinases in pluripotency regulation has not been systematically evaluated
- In a screen for modifiers of the naive-primed transition, we uncover XMD series compounds, which selectively inhibit the Erk5 kinase

□ **Treatment for breast and prostate cancer**

- During the early stages of breast cancer, ERK5 expression was detected in the majority of patients, with overexpression occurring in approximately 20% (HER2 overexpression is detected in 20–30% of breast carcinomas..). A potential role for ERK5 in chemoresistance in breast cancer has been identified in recent studies
- ERK5-overexpressing PC3 cells had significantly increased levels of proliferation, and invasion (emphasizing the relationship between ERK5 and the aggression of prostate cancer)

□ **Competitive advantage:**

- First class of Erk5 inhibitors had an off-target effect on Brd4 and many biological effects were Brd4-dependent; JGG045 and JWG071 are newly developed Erk5 inhibitors with Erk5 selectivity
- Competition : BIX02188 and BIX02189 (developed by Boehringer Ingelheim for MEK5, only upstream kinase, inhibition) XMD8-92 (Inhibition of EGF-induced activation of ERK5, Script)

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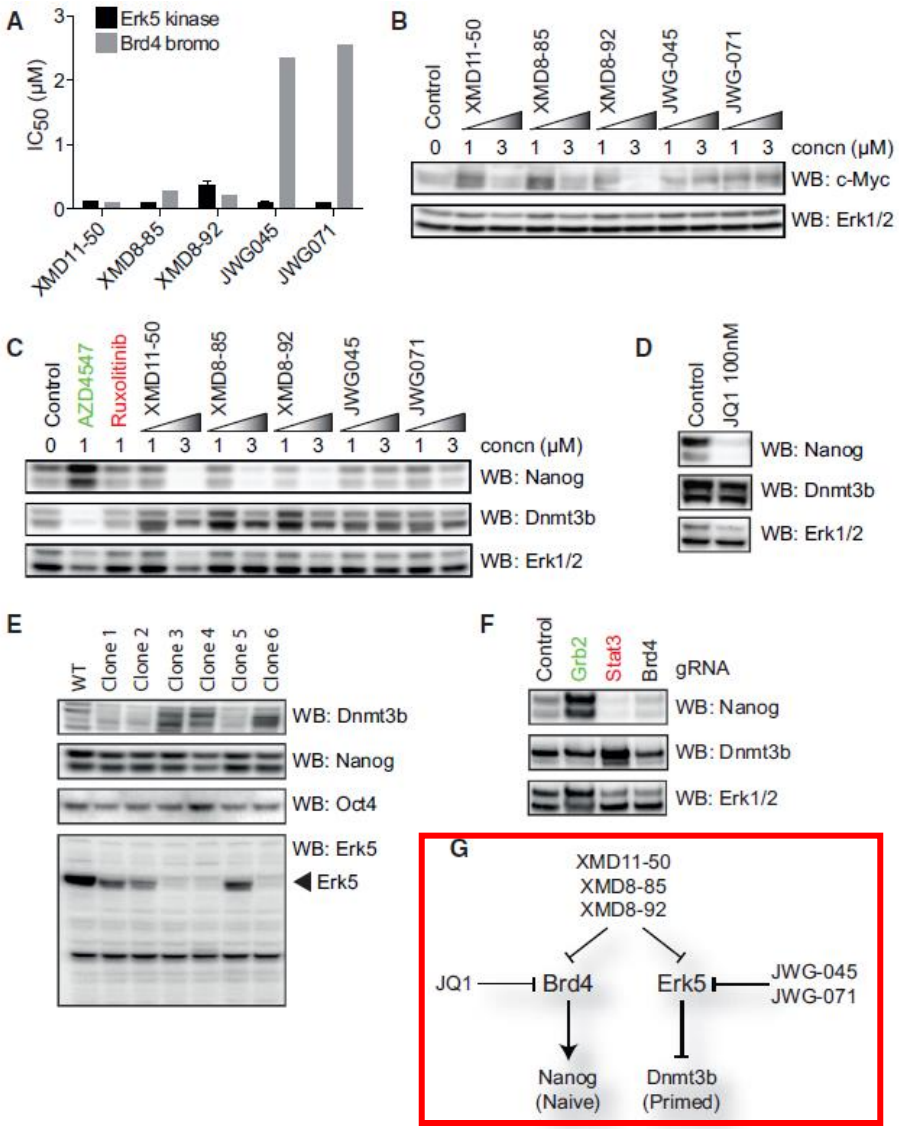
▶ Key Data

Deconvolution of Distinct Functions for Erk5 and Brd4 in Pluripotency



(A) IC50 determination for inhibition of Erk5 and Brd4 by XMD and JWG compounds.

(B) mESCs were treated with the indicated concentrations of XMD and JWG inhibitors, and c-Myc

(C) 1 mM AZD4547 or ruxolitinib or the indicated concentrations of XMD and JWG inhibitors.

(D) mESCs were treated with 100 nM JQ1 and Nanog, Dnmt3b, and Erk1/2 levels

(E) Erk5 gene targeted mESC clones were generated using CRISPR/Cas9 D10A. Dnmt3b, Nanog, Oct4

(F) mESCs were transiently transfected with Cas9 D10A and either control

(G) Deconvolution of the role of Erk5 and Brd4 in pluripotency regulation.

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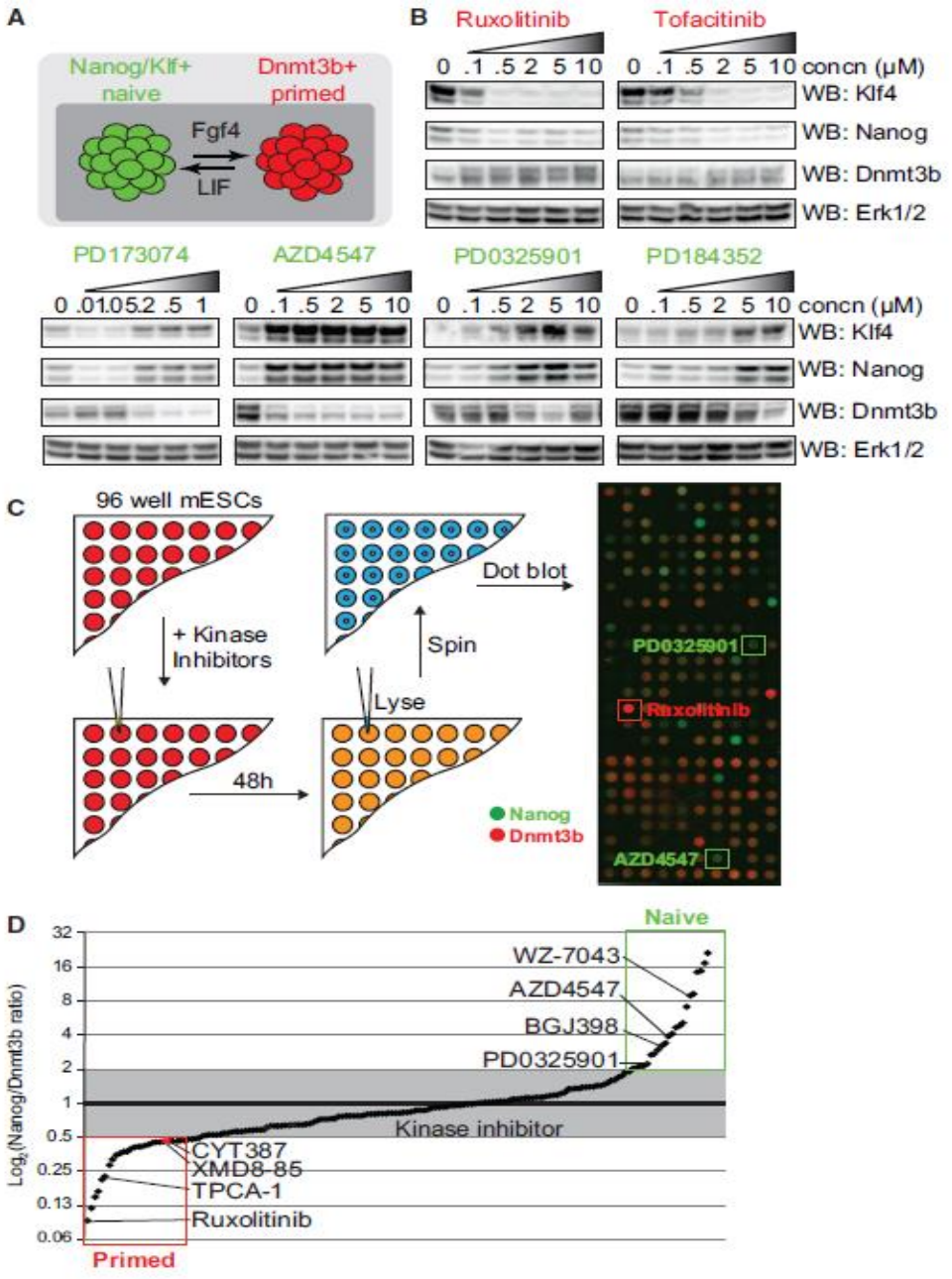
Systematic Identification of Kinase Inhibitors that Modulate Naive-Primed Pluripotent Transition



(A) mESCs cultured in LIF/FBS transitioning between naive (green) and primed (red) pluripotent states. (B) mESCs were treated with the indicated concentrations of Jak inhibitors (ruxolitinib and tofacitinib), Fgfr inhibitors (PD173074/AZD4547), or Mek1/2 inhibitors (PD0325901/PD184352). (C) 228 potent and selective kinase inhibitors were screened at 1 mM for effects on pluripotency signature. (D) The Nanog:Dnmt3b ratio for each kinase inhibitor was determined and inhibitors ranked accordingly.

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Intellectual Property

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Country	PCT, US, EP, JP, CA

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