Results and Methods

• Engagement of the T-cell receptor (TCR) in malignant T-cells leads to

• ITK and resting lymphocyte kinase (RLK) are partially redundant TEC

heterogeneous subtype of non-Hodgkin lymphoma

family kinase members involved in TCR signaling2.

the ITK-specific inhibitor CPI-818 (ITKi) and the dual ITK/RLK inhibitor

or inhibition of ITK1.

interleukin-2-inducible T-cell kinase (ITK) dependent activation of NF-

κB and GATA3, and promotes chemotherapy resistance1.

Figure 1: CPI-818 and CPI-893 inhibit TCR signaling

ITK (n=3/3) and low level RLK in a single case that was seen only on overexposure of the blot [“RLK(long)”.

blotting. Normal T cells expressed both ITK and RLK (n=3/3) while malignant T cells preferentially expressed

involvement by TCL were purified using CD3 positive selection followed by protein isolation and western

presence of 1

Nuclear and cytoplasmic fractionation. Western blot was performed on each fraction for p65. ITK inhibition with

Figure 2: CPI-818 has minimal effect on normal T cells

(A) Peripheral blood T cells from healthy donors were isolated by negative selection. TCR stimulation with

(B) IL-10 concentration in cell culture supernatants was evaluated by ELISA after 24 hours with and

without TCR stimulation (anti-CD3/CD28 beads – “B”). CPI-893 (ITK/RLKi), but not CPI-818 (ITKi)

impairment of malignant T cells almost exclusively express ITK, or express RLK at very low levels

Conclusions

• CPI-818 is a potent ITK specific inhibitor, while CPI-893 inhibits both

ITK and RLK.

• Normal T cells express both ITK and RLK which can compensate for

inhibition of ITK function.

• Malignant T cells almost exclusively express ITK, or express RLK at very low levels.

• CPI-818 impairs TCR signaling resulting in:

• Impaired malignant T cell growth and proliferation

• Increased chemosensitivity

• Decreased GATA3 expression

• CPI-818 has minimal effect on normal T cells

Future Directions

• Collectively, our data support further preclinical and clinical studies with CPI-818 in T-cell lymphoproliferative disorders.

References


Disclosures

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