HIGHLY SELECTIVE IRREVERSIBLE ITK INHIBITOR CPI-818 REDUCES ACUTE GRAFT-VERSUS HOST DISEASE

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INTRODUCTION

- Acute graft-versus-host disease (aGVHD) remains a major limitation of allogeneic hematopoietic cell transplantation (allo-HCT) despite prophylactic immunosuppression; not all patients who develop aGVHD respond to currently available treatment[1].
- Interleukin-2-Inducible T-Cell Kinase (ITK) is a non-receptor tyrosine kinase with an important role in T cell activation (**Fig. 1a**) and targeting ITK has been shown to be associated with less GVHD[2,3].
- CPI-818 is a highly selective ITK inhibitor (**Fig. 1 b and c**) and is currently being evaluated in patients with relapsed/refractory T-cell lymphoma (NCT03952078)

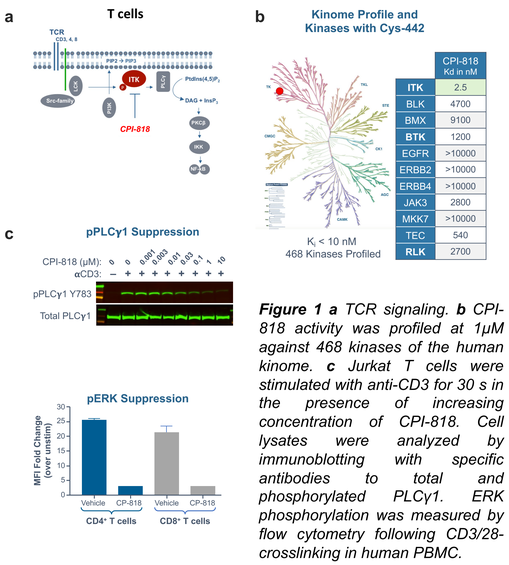


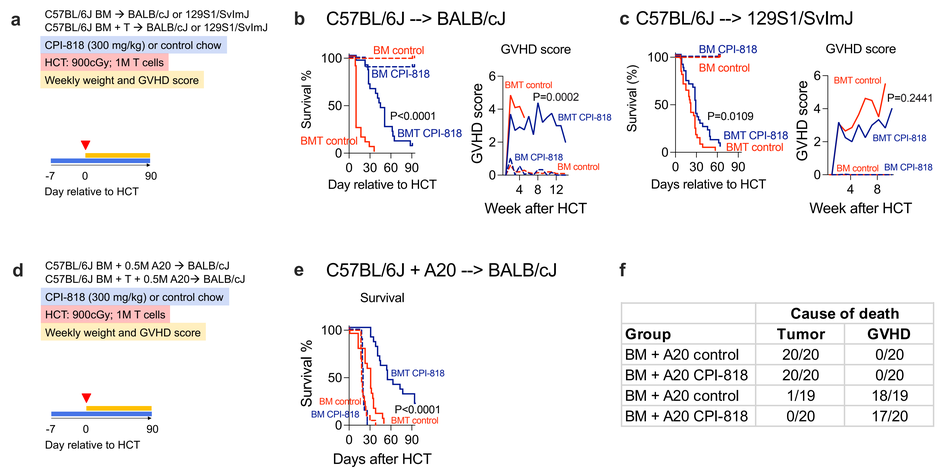
Figure 1 *a TCR signaling.* ***b*** *CPI-818 activity was profiled at 1μM against 468 kinases of the human kinome.* ***c*** *Jurkat T cells were stimulated with anti-CD3 for 30 s in the presence of increasing concentration of CPI-818. Cell lysates were analyzed by immunoblotting with specific antibodies to total and phosphorylated PLCγ1. ERK phosphorylation was measured by flow cytometry following CD3/28-crosslinking in human PBMC.*

AIM

To study the effect of ITK inhibition by CPI-818 in preclinical mouse models of GVHD.

RESULTS

CPI-818 treatment reduces GVHD and improves survival



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	Cause of death	
Group	**Tumor**	**GVHD**
BM + A20 control	20/20	0/20
BM + A20 CPI-818	20/20	0/20
BM + A20 control	1/19	18/19
BM + A20 CPI-818	0/20	17/20

Figure 2 *HCT recipient were treated with CPI-818 formulated (300mg/kg) or control diet starting D-7 until D90 relative to HCT* ***a*** *Schematic GVHD model* ***b*** *Survival and clinical GVHD score of BALB/cJ recipients after lethal irradiation and C57BL/6N HCT (MHC-disparate)* ***c*** *Survival and clinical GVHD score of 129S1/SvImJ recipients after lethal irradiation and C57BL/6N HCT (minor MHC-mismatched) and* ***d*** *Schematic GVT model* ***e*** *Survival and cause of death of BALB/cJ recipients after lethal irradiation and C57BL/6N HCT + lymphoma cell line A20. Survival data were statistically analyzed using Mantel-Cox log-rank test. GVHD score data were statistically analyzed using the Velardi test, n = 10-30 mice per group. All results are from two or three independent experiments.*

CPI-818 treatment supresses T cell proliferation and activation and increases regulatory T cells in GVHD

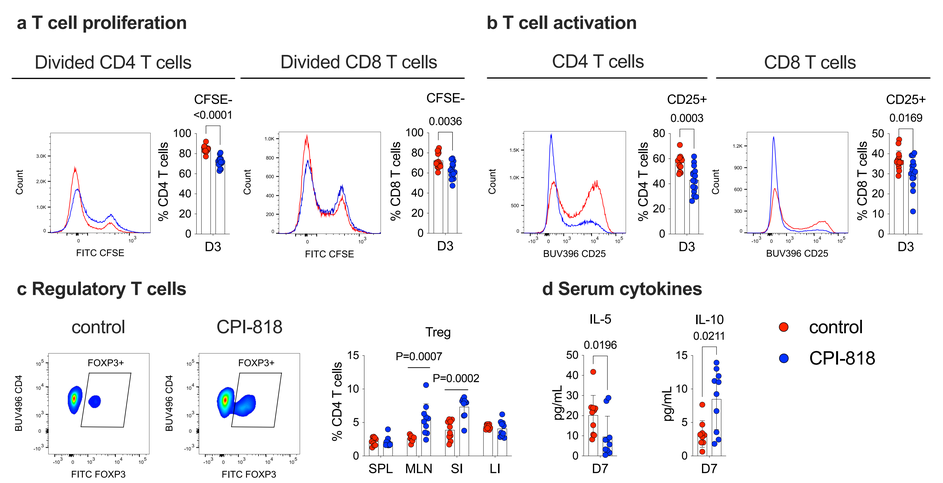

Figure 3 *BALB/cJ recipients after lethal irradiation and C57BL/6N HCT with either 5x10⁶ CFSE labeled T cells (harvest D3) or 1x10⁶ T cells (harvest D7) and were treated with CPI-818-formulated (300 mg/kg) or control diet from D-7 relative to allo-HCT to harvest day.* ***a*** *Representative histogram of CFSE (red: control and blue: CPI-818) and CFSE- percentages* ***b*** *Representative histogram of CD25 (red: control and blue: CPI-818) and percentages of CD25+ are shown from spleen on D3 post allo-HCT.* ***c*** *Representative flow dot plot from MLN and FOXP3+ percentages are shown from SPL, MLN, SI and LI on D7* ***d*** *Serum cytokines were measured at D7 post allo-HCT. All comparisons were performed by two-tailed unpaired Mann-Whitney Test. Values are means ± standard deviation, n = 10-20 mice per group. All results are from two independent experiments.*

CONCLUSIONS

- ITK inhibition has potential as a novel targeted approach to prevent aGVHD through
  a) the suppression of early T cell activation and proliferation
  b) decreased concentrations of pro-inflammatory cytokines, increased concentration of anti-inflammatory cytokines and increased regulatory T cells
- CPI-818 is the most potent and selective ITK inhibitor reported to date and these data highlight its promise as a novel agent for the prevention of aGVHD.

REFERENCES

1. Zeiser R, Blazar BR. Acute Graft-versus-Host Disease - Biologic Process, Prevention, and Therapy. N Engl J Med. 2017;377(22):2167-79.
2. Mammadli M et al. Targeting Interleukin-2-Inducible T-Cell Kinase (ITK) Differentiates GVL and GVHD in Allo-HSCT. Front Immunol. 2020;11:593863.
3. Kondo T et al. Pretransplant Short-Term Exposure of Donor Graft Cells to ITK Selective Inhibitor Ameliorates Acute Graft-versus-Host Disease by Inhibiting Effector T Cell Differentiation while Sparing Regulatory T Cells. Immunohorizons. 2021;5(6):424-37.

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