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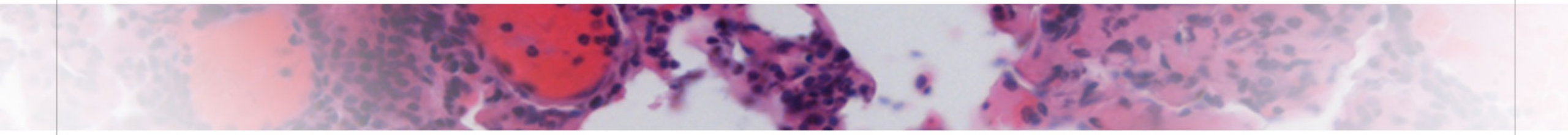

The ITK Inhibitor CPI-818 Blocks Activation of T Cells from Autoimmune Lymphoproliferative Syndrome (ALPS) Patients and is Active in a Murine Model of ALPS

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Disclosures
VKR – Research Support from Novartis through CRADA for unrelated projects.
PN, CH, RM, JB and JJ are employees and stock holders of Corvus Pharmaceuticals.

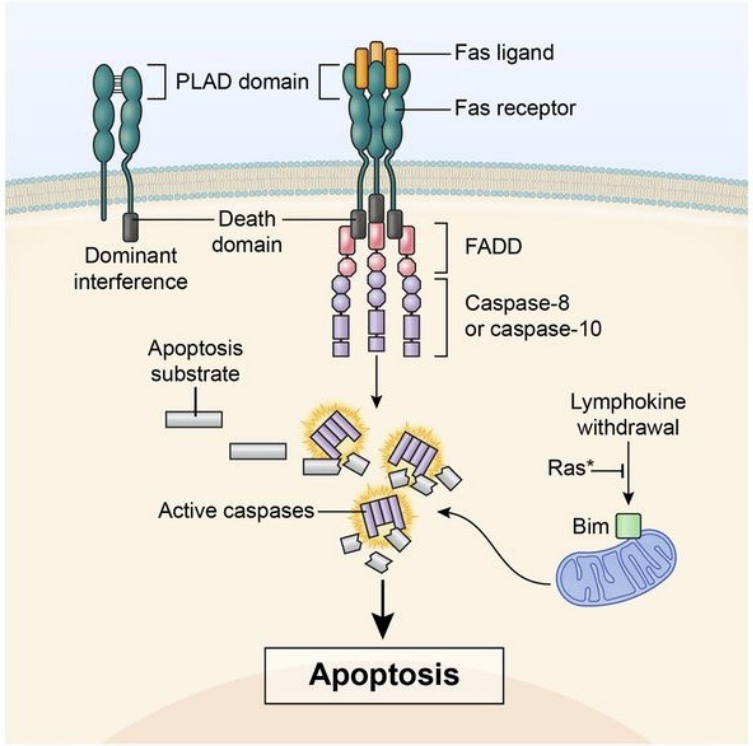
ALPS was recognized as a distinct entity in NIAID-NIH in 1990s

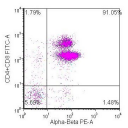
1946-2007

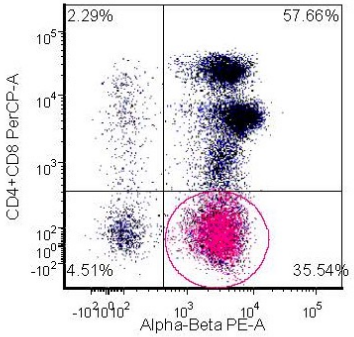
ALPS was recognized as a distinct entity among the patients referred to rule out EBV driven LPD by Dr. Stephen Straus at NIAID.

Autoimmune Lymphoproliferative Syndrome (ALPS)

- FAS mediated disorder of lymphocyte apoptosis leads to lymphocyte accumulation
- Pathophysiology is driven by germline and somatic heterozygous variants in *FAS*
- Leads to childhood onset lymphadenopathy, hypersplenism, and refractory multi-lineage cytopenias
- Increased risk of lymphoma
- *Imperative to save the spleen due to significant risk of infections post-splenectomy (OPSI)*







Current therapies are focused towards steroid and spleen sparing immunosuppressive regimens for ALPS-associated autoimmunity

New targeted treatments are needed to reverse lymphoproliferation, adenopathy and splenomegaly

Key References:

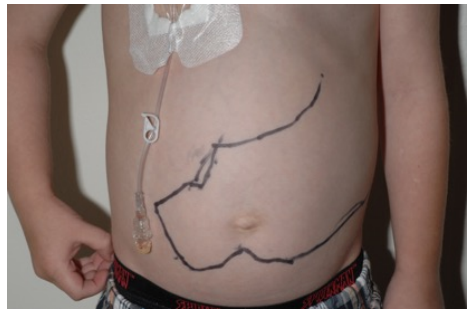
MRL/lpr mice: Watanabe-Fukunaga et al. Nature, 1992
Human ALPS: Sneller MC et al. JCI, 1992 , Blood, 1997
ALPS Workshop: Blood. 2010 Jun 10. PMID: 20538792
Natural History of ALPS: Blood 2014.

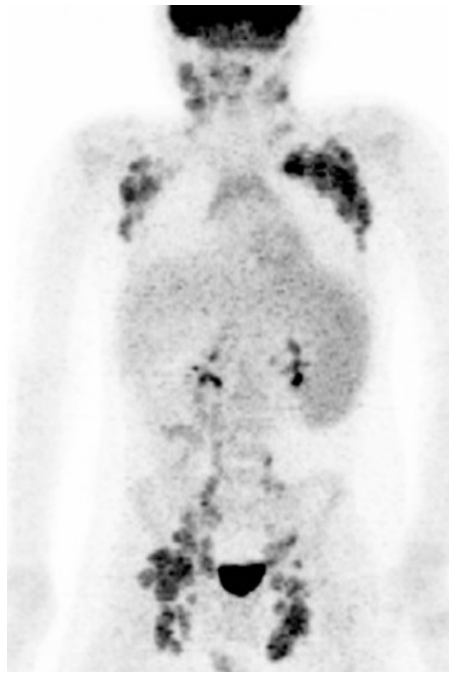
Evolving paradigms of management of B cell driven pathobiology due to T cell dysfunction in ALPS: 1990s - 2020

- Since 1993, 220 ALPS-FAS patients and more than 400 families with ALPS like disorders with non-malignant lymphoproliferation have been followed at NIH ALPS Clinic as part of family-studies
- Though splenectomy was the go-to remedy until early 2000s for refractory cytopenias; advent of steroid and spleen sparing immunomodulatory regimens have been the mainstay recently:

  mycophenolate mofetil(MMF), rapamycin

  rituximab, plaquenil, TPO-mimetics
- ALPS-FAS illustrates importance of apoptosis in remodelling the lymphocyte repertoire and deleting cells with autoimmune and oncogenic potential

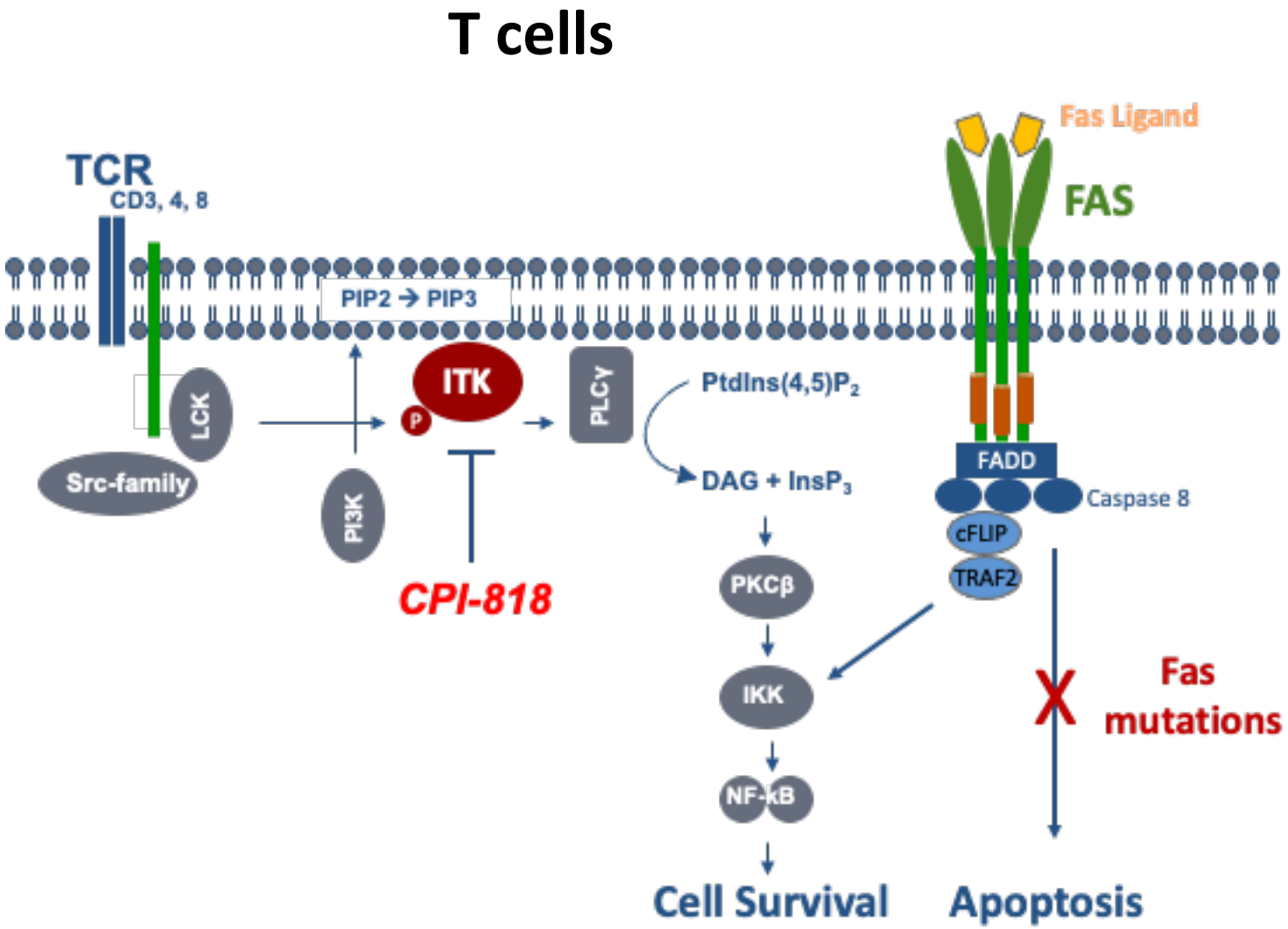




- Can it be amenable to emerging targeted therapies

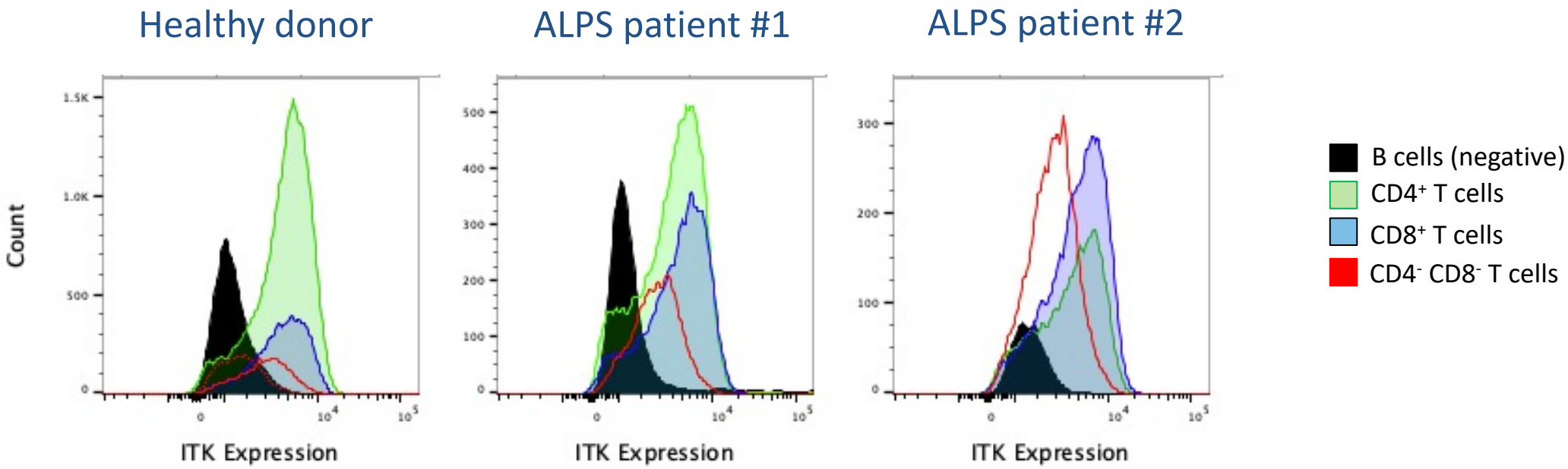
Rao, Straus et al: Use of MMF in ALPS: BJH 2005
Rao and Oliveira: How I Treat ALPS: Blood 2011, 2015
Rao: ASH 2018 and Frontiers in Pediatrics July 2015

FAS and T cell receptor (TCR) signaling are linked



- TCR and FAS pathways modulate an equilibrium between proliferation and activation-induced cell death
- **ITK** is a key enzyme in the TCR pathway and provides a convenient drug target
- Hypotheses
  - Dysregulated growth of Fas-deficient T cells requires functional TCR signaling
  - Pharmacologic ITK inhibition may restore apoptosis in the absence of Fas by blocking TCR-driven cell survival signals

ITK is expressed similarly in both normal and ALPS T cells



ITK expression pattern is similar in PBMCs from ALPS patients compared to a healthy donor

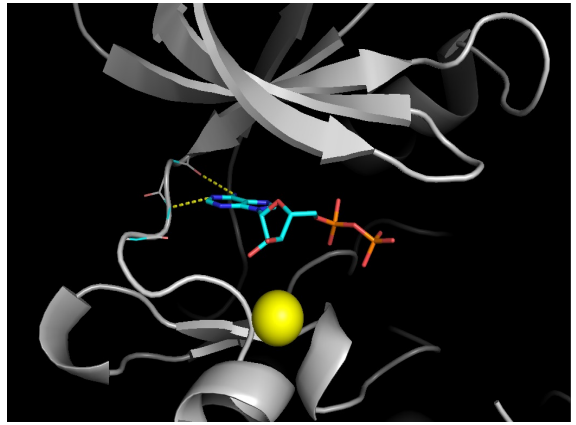
ITK detected in $CD4^+$, $CD8^+$, and double-negative ($CD4^-$, $CD8^-$) T cells

No ITK expression in B cells, as expected

CPI-818: a selective and irreversible inhibitor of ITK in Phase I clinical development

CPI-818 selectively inhibits ITK

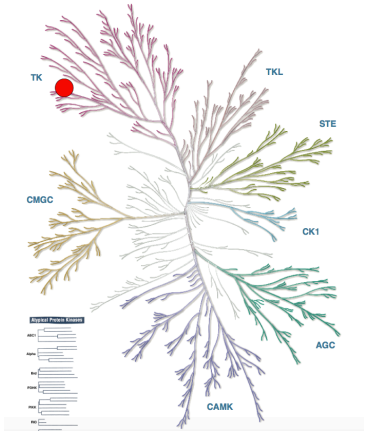
- Covalent mechanism, targets cysteine at active site
- Similar mechanism to BTK inhibitor, ibrutinib



CPI-818 in a Ph I study in T cell lymphoma

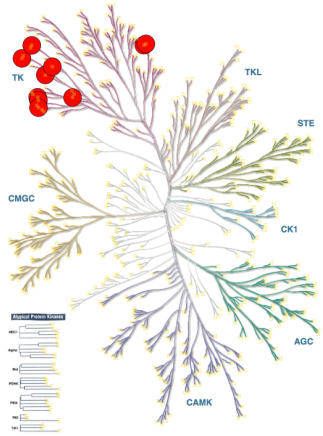
- Oral administration, BID Dosing
- Safe dose established with full ITK inhibition
- No opportunistic infection related SAEs
- Complete and partial responses observed in patients with T cell lymphomas
- See ASH **Poster 2068**

CPI-818



● K_i < 10 nM, 468 Kinases Profiled

Ibrutinib

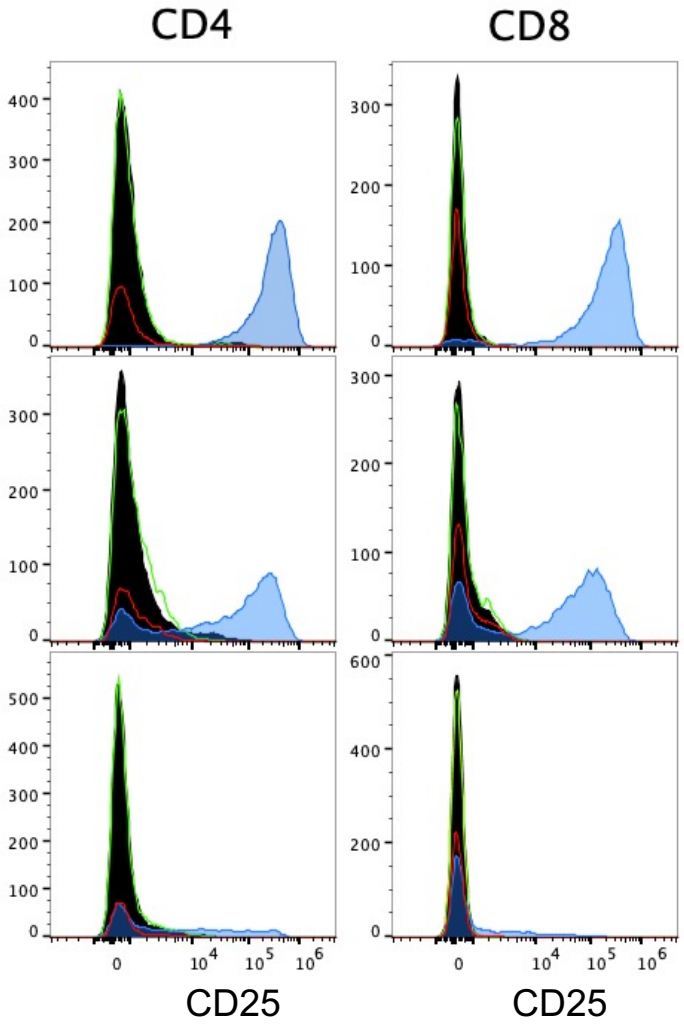


● K_i < 10 nM, Honigberg (2010) PNAS

Sunitinib

Karaman (2008) Nat. Biotech.

CPI-818 inhibits activation of stimulated T cells in ALPS patients



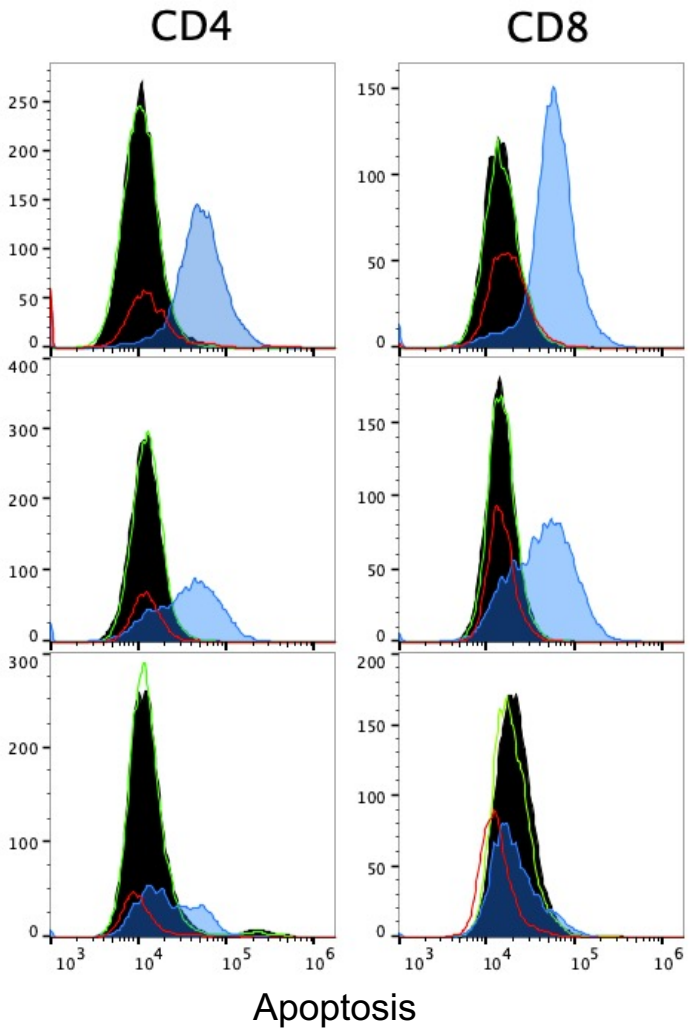
TCR stimulation (anti-CD3/CD28) led to activation of T cells (CD25) in healthy donor and one of two ALPS patients

CD25 expression was fully blocked by ITK inhibition with CPI-818

CPI-818 was not cytotoxic to cells

Similar results were observed using CD69 as activation marker

CPI-818 inhibits T cell activation-induced cell death



PBMCs from healthy donor and one of two ALPS patients could elicit AICD

ITK inhibition by CPI-818

- Blocked AICD
- Did not induce apoptosis in unstimulated cells

Evaluation of CPI-818 in Fas-deficient mice (MRL/*lpr*$^{-/-}$)

CPI-818 inhibits lymphadenopathy and proteinuria in lpr mice (STUDY 1)

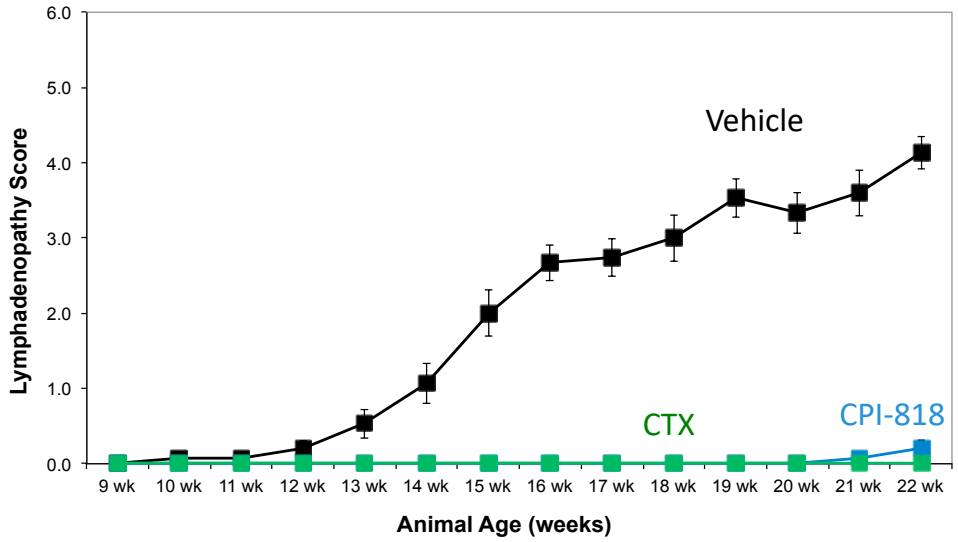
Fas-deficient (*lpr*) mice considered an *in vivo* model of ALPS

- Expansion of double-negative (CD4−CD8−B220+) T cells, Massive lymphadenopathy, Autoimmune manifestations
  Kidney failure

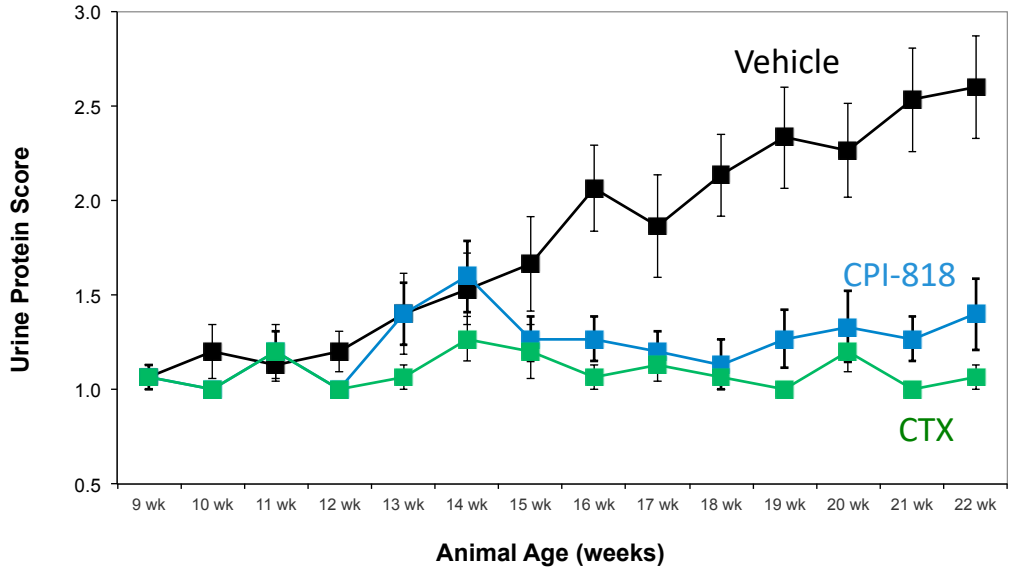
Evaluation of ITK inhibition

Mice developed lymphadenopathy at 10-12 weeks, Administered CPI-818 formulated in the mouse chow
STUDY1 (prophylactic): drug introduced week 9

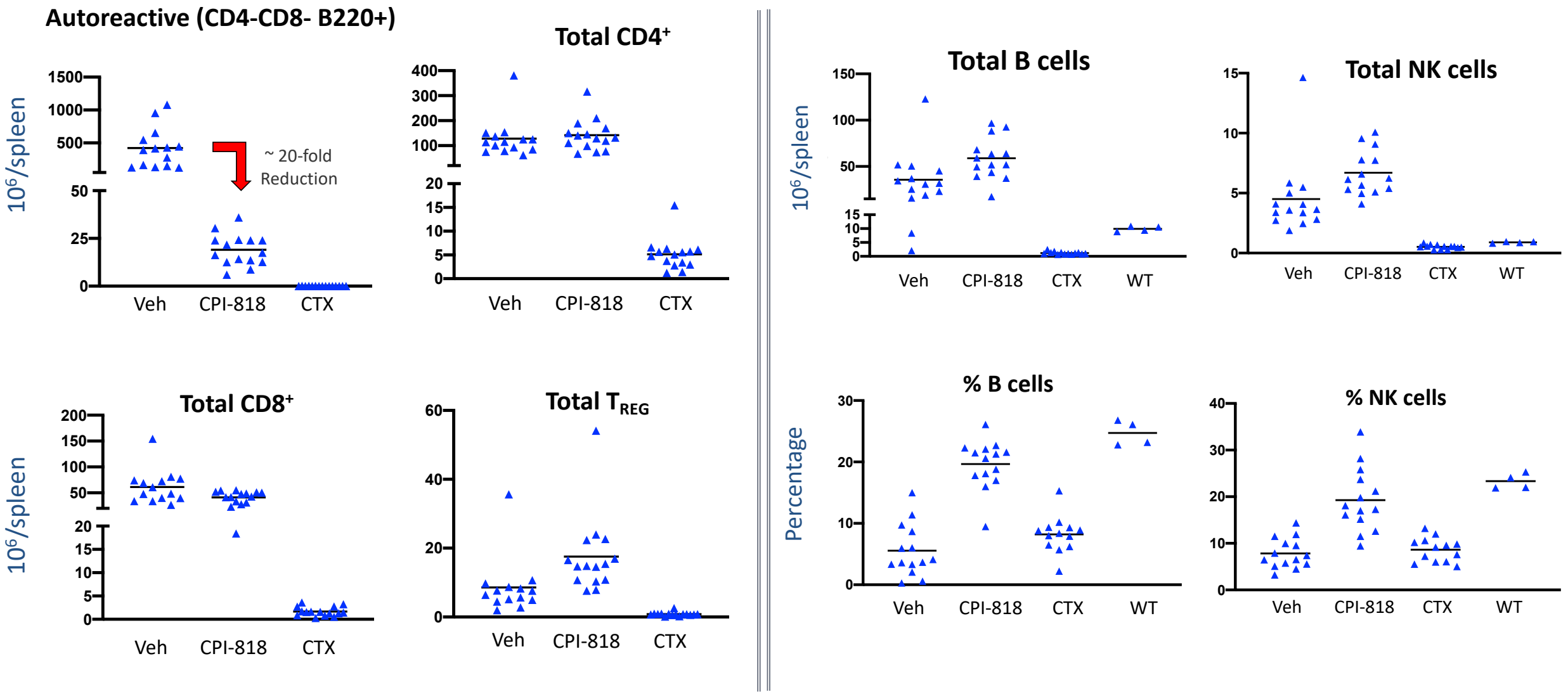
Reduction in Lymphadenopathy



Reduction in Proteinuria



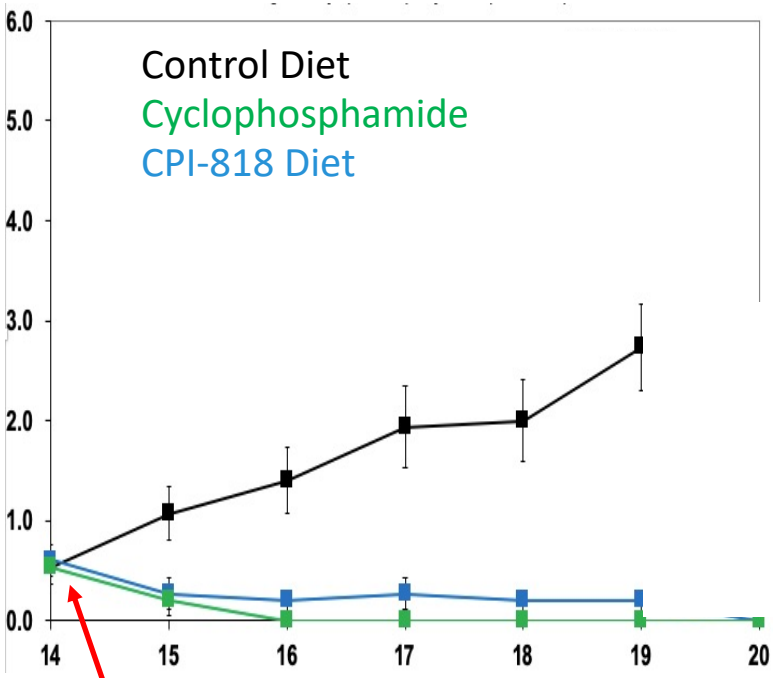
CPI-818 selectively inhibits CD4-CD8- DN T cell expansion in the spleen and restored normal proportion of B and NK cells



STUDY 2: CPI-818 reduced established disease in MRL/lpr

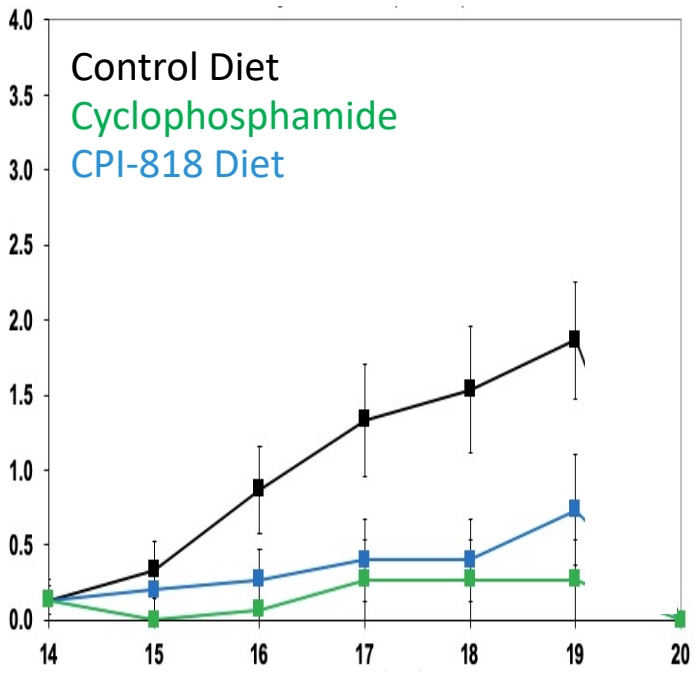
Treatment began after lymphadenopathy

Lymphadenopathy Score



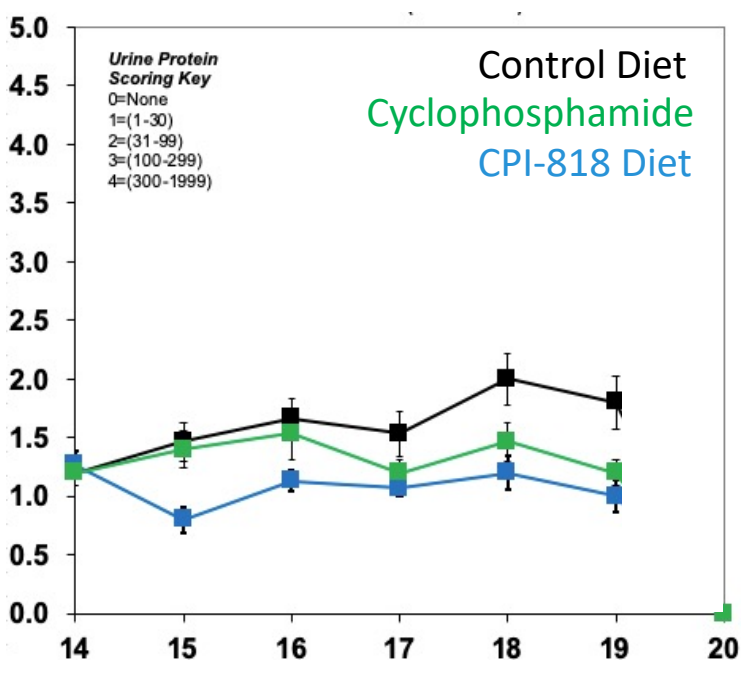
CPI-818 treatment began

Skin Lesion Score



Age (Weeks)

Proteinuria



Conclusions

- Clinical stage covalent ITK inhibitor CPI-818 in ALPS patient PBMCs
  - Was not cytotoxic
  - Inhibited T cell activation (CD25/CD69)
  - Inhibited activation-induced cell death
- In Fas-deficient (MRL/lpr-/-) mice
  - CPI-818 selectively inhibited the expansion of double-negative T cells
  - Reduced lymphadenopathy, proteinuria, and skin lesions similar to cyclophosphamide control
- These data support the evaluation of CPI-818 in a proof of principle clinical trial in patients with ALPS-FAS