A novel inhibitor of BET family bromodomains demonstrates *in vivo* and *in vitro* potency in B-cell malignancy

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Chronic Lymphocytic Leukemia (CLL)

- **Hallmarks of CLL**
  - Clonal expansion of mature B-lymphocytes
  - $CD19^{+}/CD5^{+}/CD23^{+}/CD43^{+}/CD20^{Low}$
  - Disrupted apoptosis
  - Aberrant activation of survival pathways (i.e. B-cell receptor, NFκB)
  - Vast (epi)genetic heterogeneity

- Despite recent progress with targeted therapies, CLL is still considered incurable

- Up to 10% of CLL patients develop Richter's Transformation (RT)

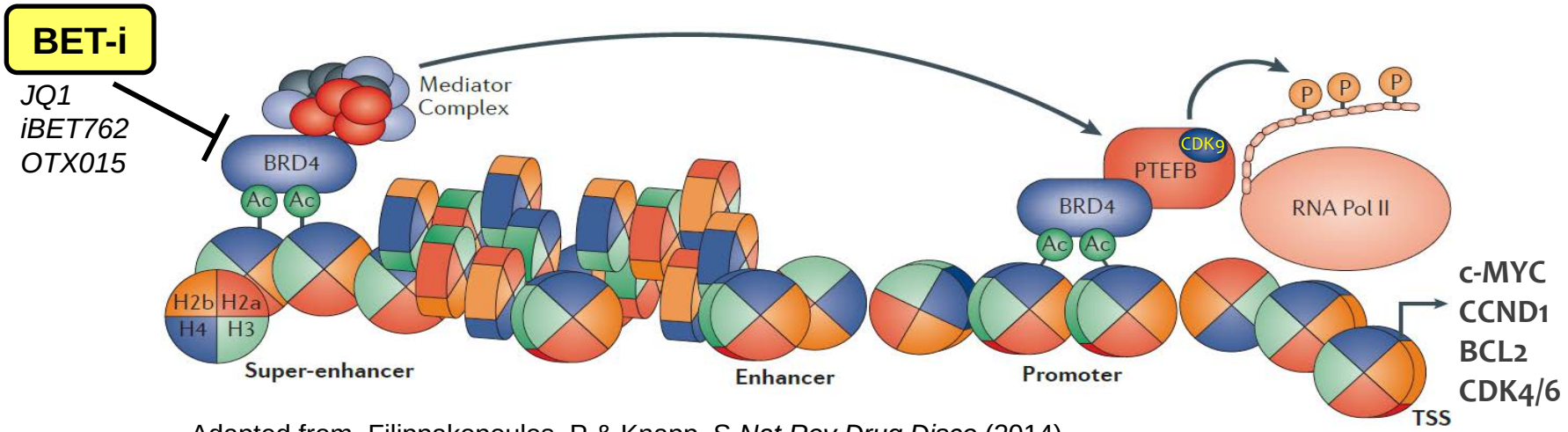
- RT is the most common progression observed in CLL patients receiving effective targeted therapy

- Growing need for **novel therapies with curative potential**

Chiorazz,i N et al. *N Engl J Med* (2005)
Burger, JA et al. *Blood (*2009)
Woyach, JA et al. *Blood* (2012)
Guièze, R & Wu, CJ *Blood* (2015)
Woyach, JA & Johnson, AJ *Blood* (2015)
Rossi, D et al. *Hematol Oncol* (2009)
Maddocks, KJ et al. *JAMA Oncol* (2015)

BET proteins: Mechanism of Actions

- BRD4 recognizes acetylated histones and recruits p-TEFb to modulate transcriptional activation of critical cell cycle and survival genes
- In cancer cells BRD4 is enriched at super-enhancer regions of oncogenes such as c-MYC, BCL2 and CDKs



Adapted from Filippakopoulos, P & Knapp, S *Nat Rev Drug Disco* (2014)

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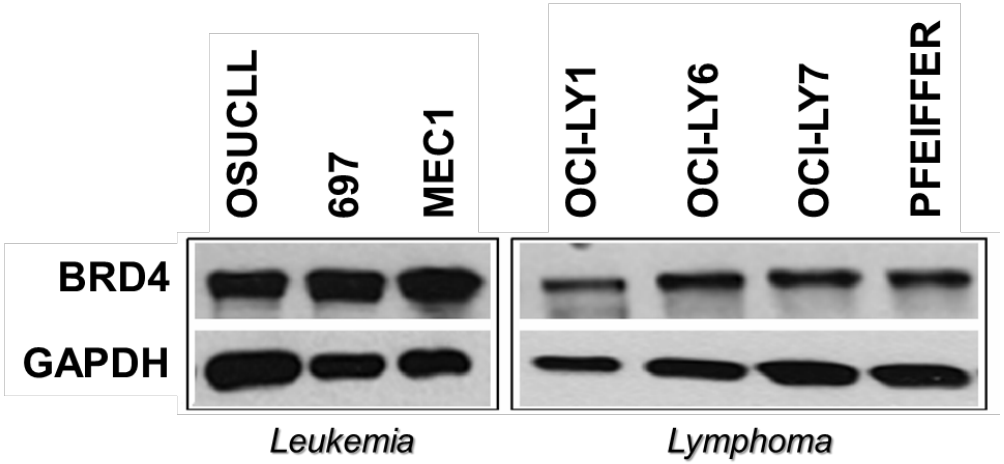
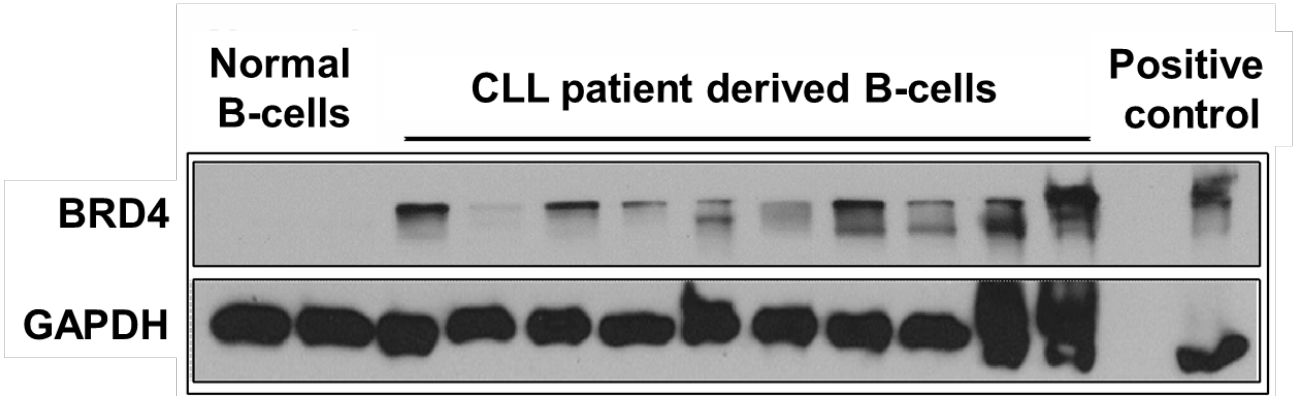
Jang, MK et al *Mol. Cell* (2005)
Yang, Z et al Mol. Cell (2005)
Chapuy, B et al *Cancer Cell* (2013)
Lovén, J et al *Cell* (2013)

BRD4 is overexpressed in CLL





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PLX51107 is a novel BET inhibitor

- Pan BET inhibitor (BRD2, BRD3, BRD4 and BRDT)
- Broad activity in Genscript's Leukemia and Lymphoma panel (IC_{50} = 0.45 µM)
- Superior pharmaceutical properties to other BET inhibitors under clinical evaluation in multiple preclinical leukemia models
- Minimal toxicity with favorable *in vivo* safety profiles
- Expected to enter human Phase I clinical trial first quarter of 2016

Mead, M et al. (UCLA); Poster # 3702

12/7/2105 from 6 - 8 pm at Hall A, Level 2

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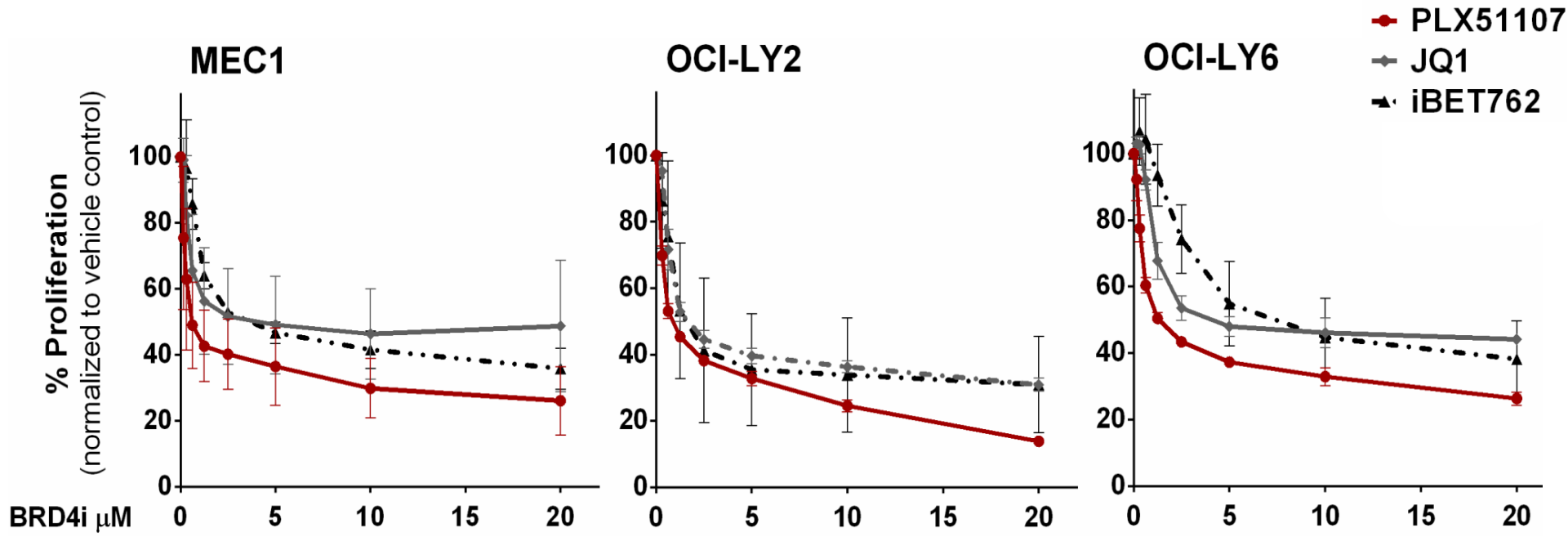
Cytotoxic effects of PLX51107 in malignant B-cells



IC_{50} (μM)			
Cell line	**PLX51107**	**JQ1**	**iBET762**
MEC1	**1.05**	4.07	4.42
OCI-LY2	**1.19**	2.62	2.31
OCI-LY6	**1.84**	5.68	8.82

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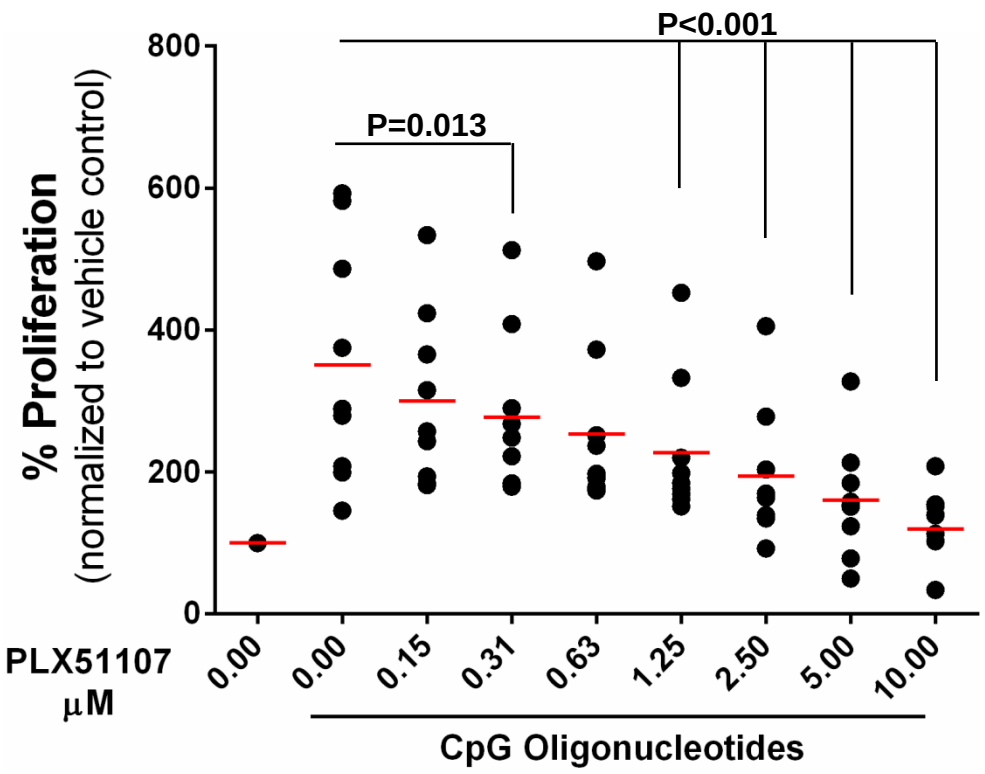
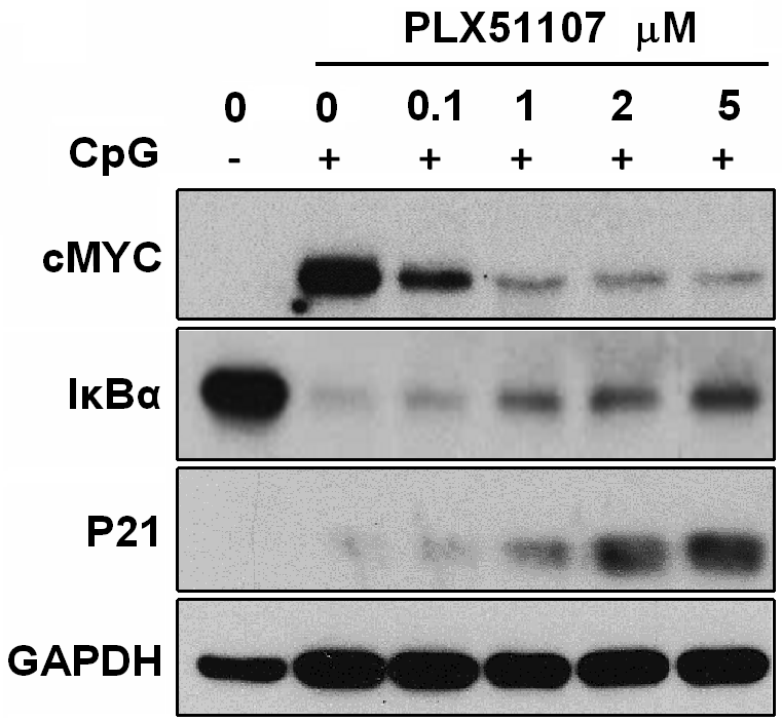
PLX51107 antagonizes CpG-induced survival in CLL cells





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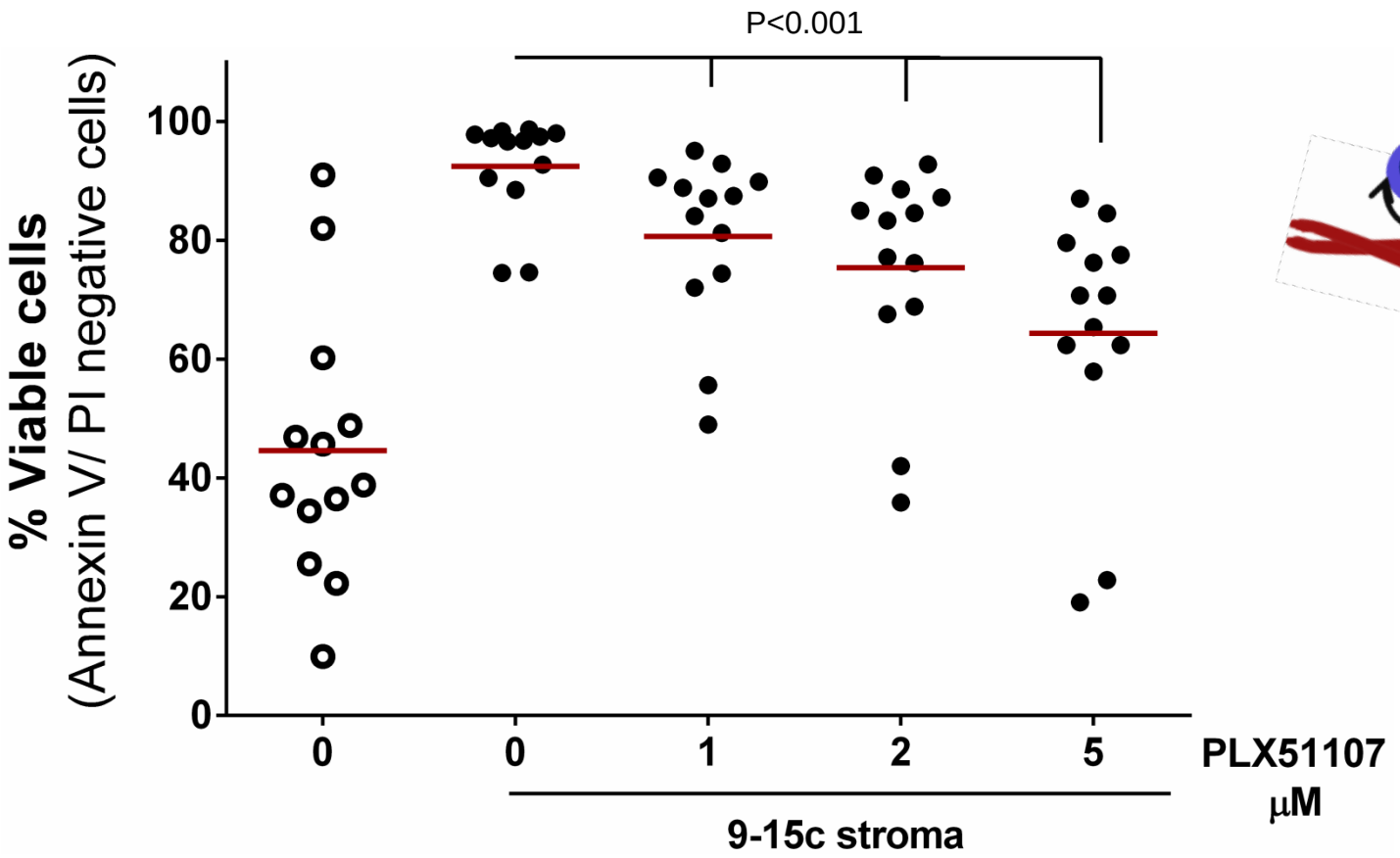
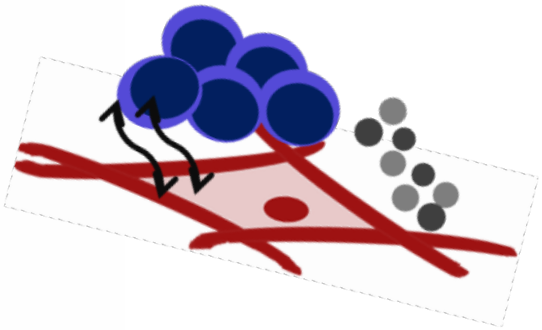
PLX51107 treatment overcomes microenvironment protection





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Eμ-TCL1 mouse model

- Human *TCL1* under the control of a B-cell specific IgV_H promoter and Ig_H-Eμ enhancer
- Develops $CD5^+/CD19^+$ leukemia similar to human CLL (9-12 months)
- High WBC counts, splenomegaly
- Responds clinically to therapeutic agents used in CLL such as ibrutinib (BTK inhibitor) and JQ1 (BET inhibitor)

Bichi, R and Croce, CM et al. *Blood* (2002)
Woyach, JA et al. *Blood* (2014)
Larsson, CA et al. ASH (2013)

PLX51107 reduces leukemic disease burden in Eμ-TCL1 mouse model of CLL

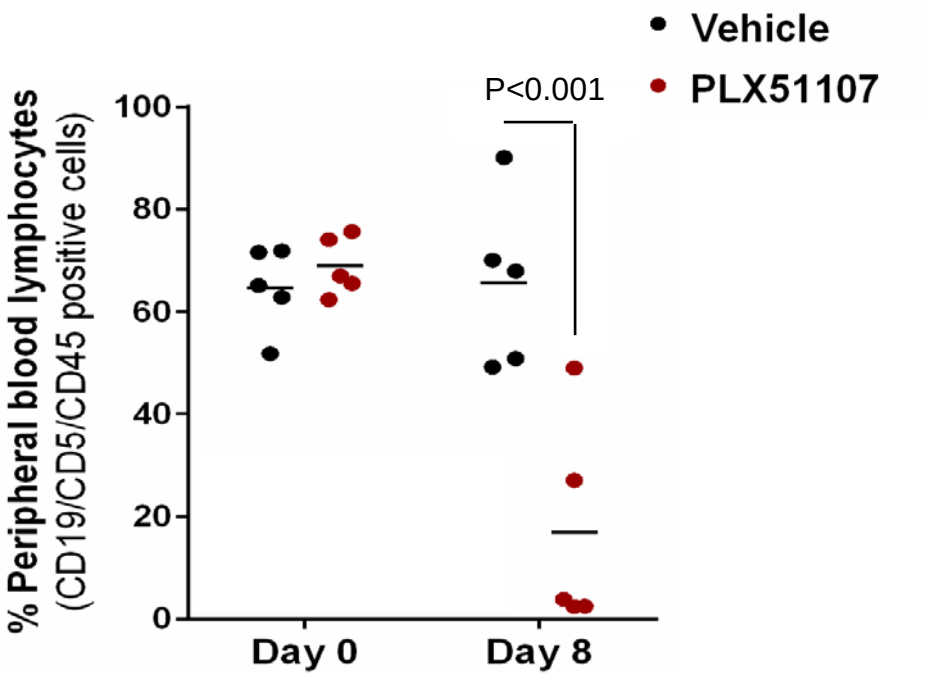
Eμ-TCL1

- >50% circulating $CD19^+/CD5^+/CD45^+$
- WBC > 60
- Splenomegaly

Vehicle

PLX51107
20 mg/kg, qd

8 days



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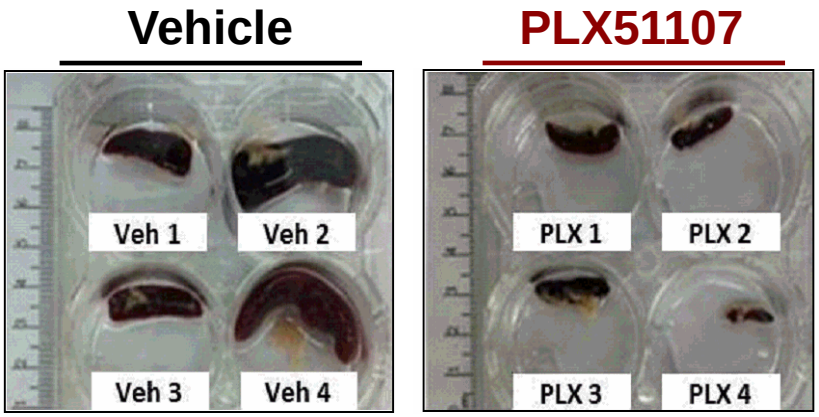
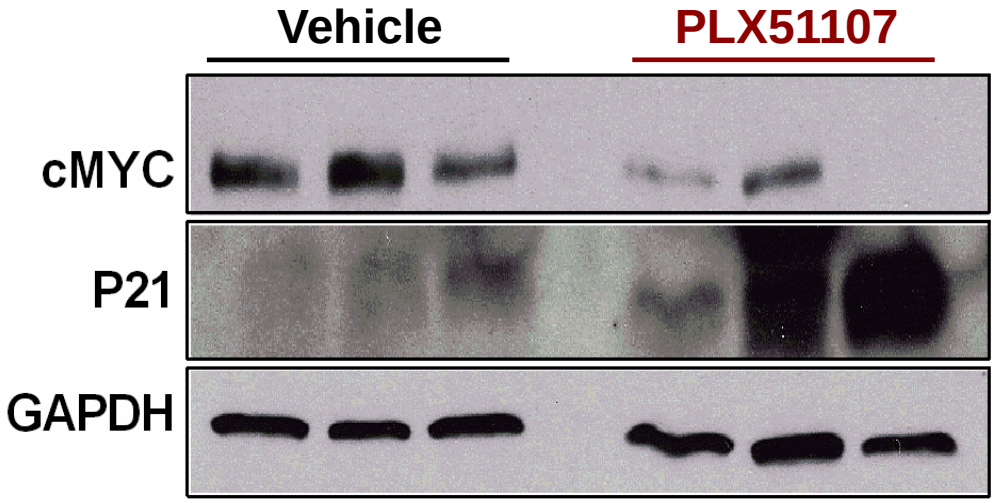
PLX51107 reduces leukemic disease burden in Eμ-TCL1 mouse model of CLL





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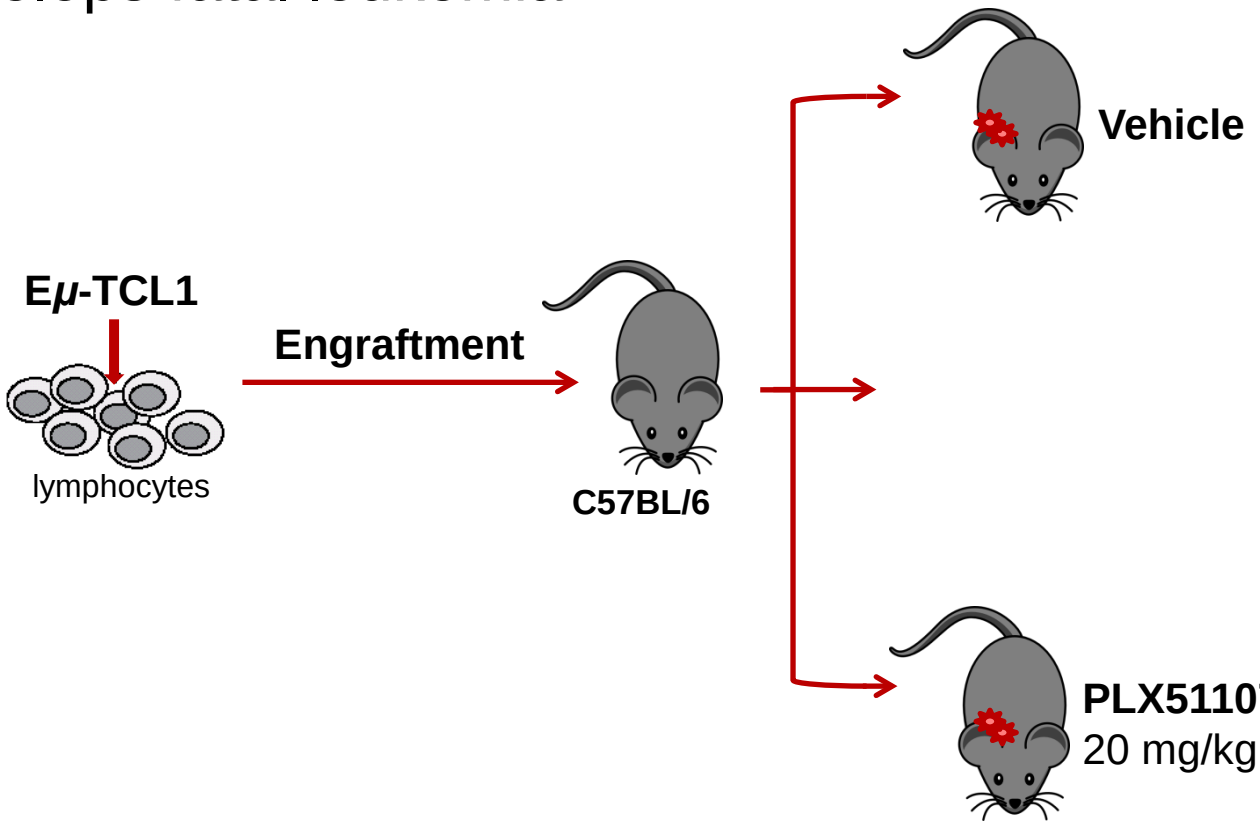
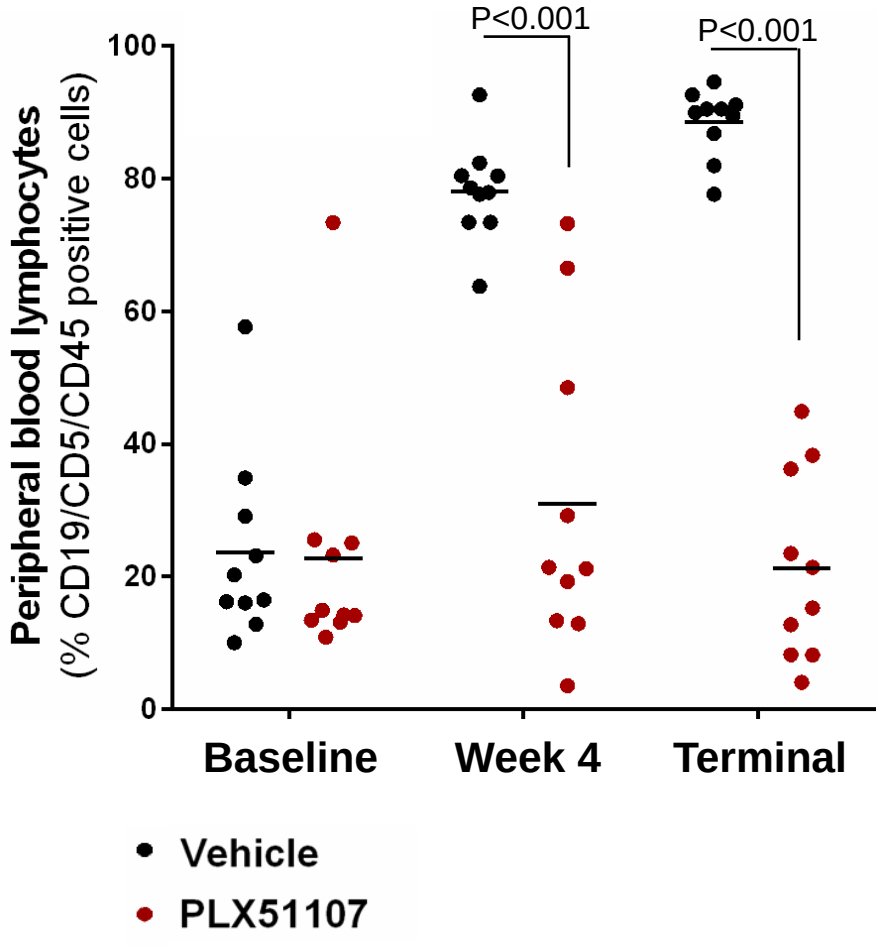
Eμ-TCL1 adoptive transfer model

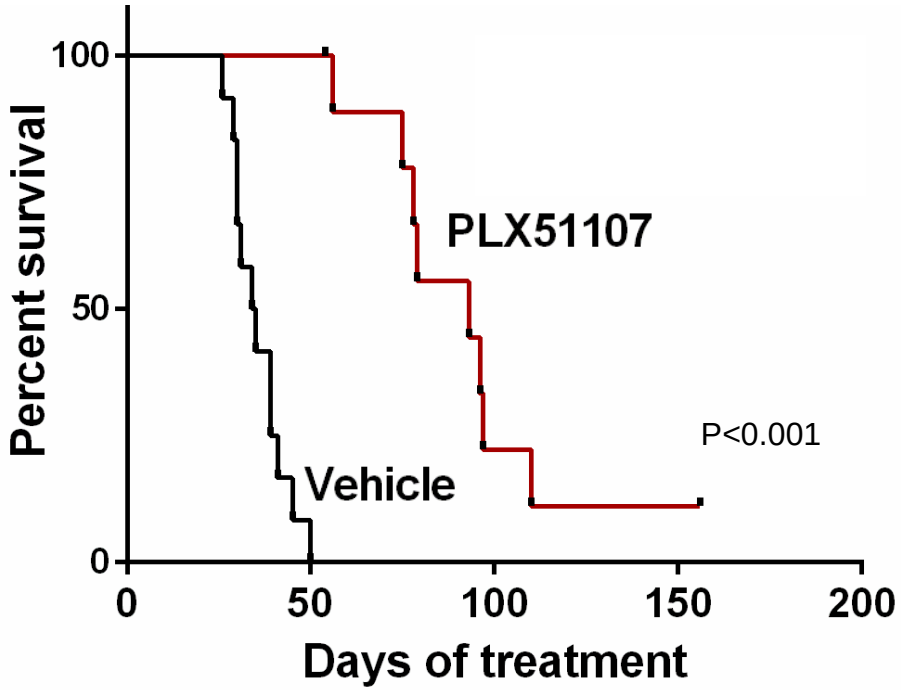
- Suitable model for pre-clinical drug testing
- Displays clinical features of aggressive CLL
- Develops fatal leukemia



Johnson, AJ et *Blood* (2006)

PLX51107 enhances survival in E*μ*-TCL1 adoptive transfer model of CLL





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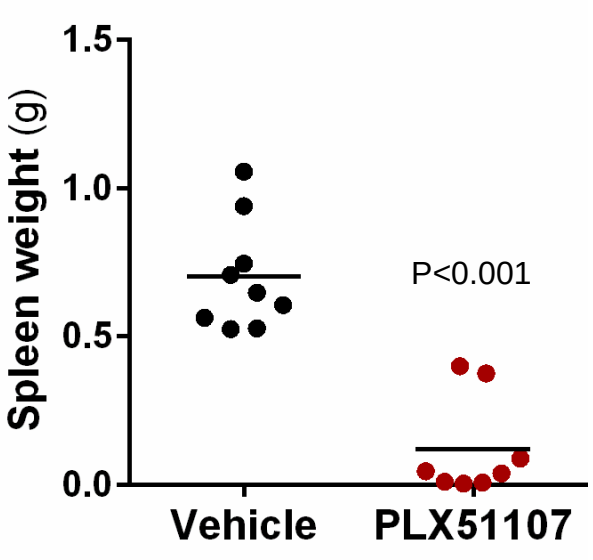
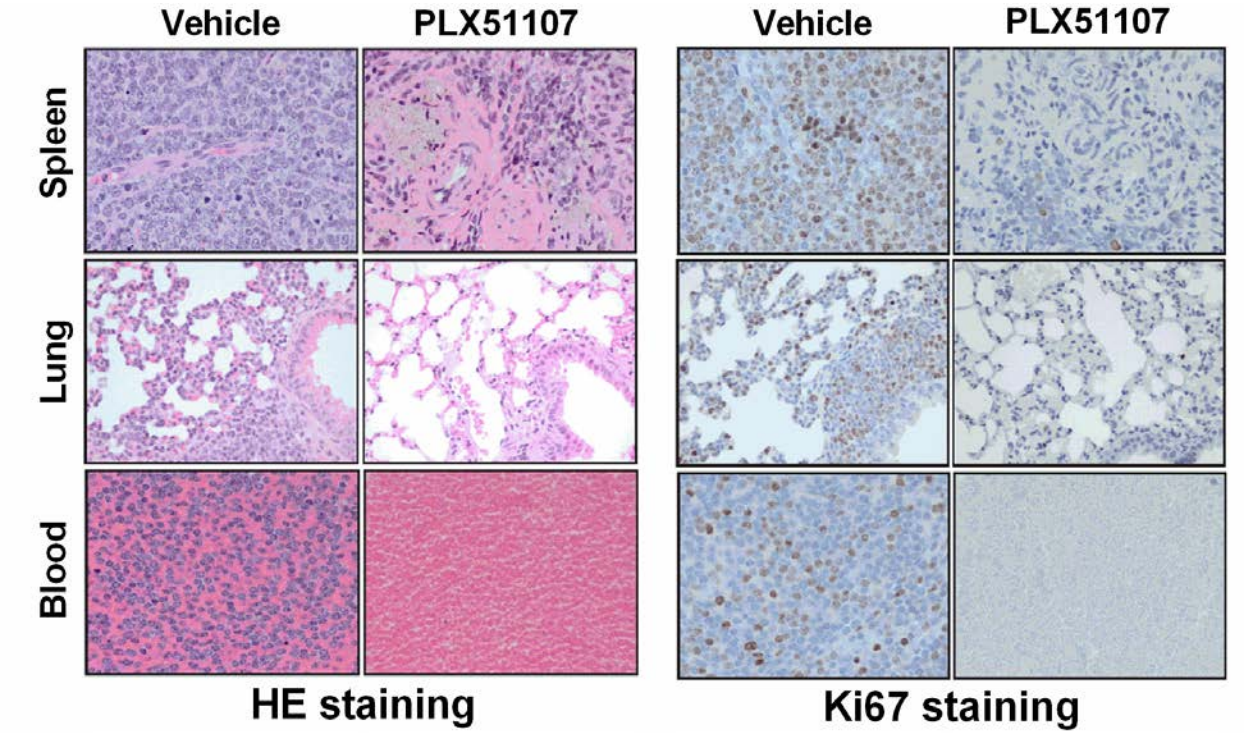
PLX51107 enhances survival in Eμ-TCL1 adoptive transfer model of CLL





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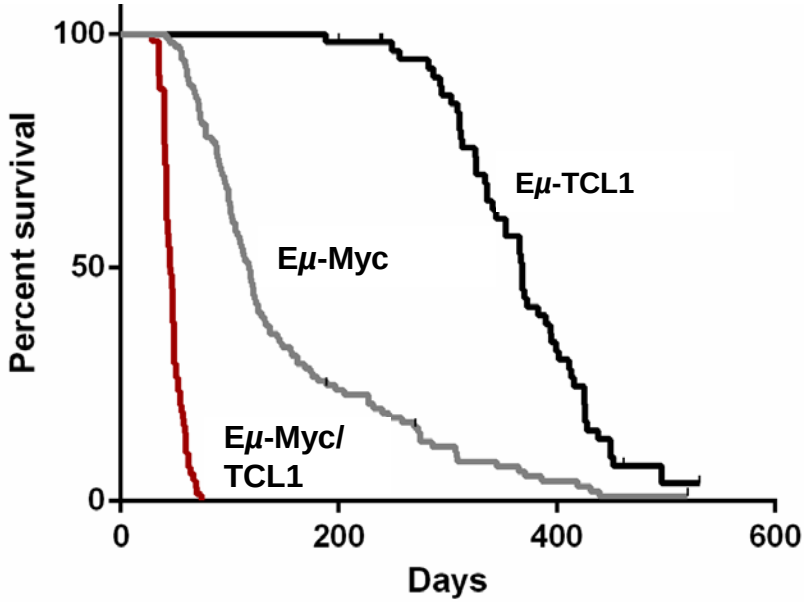
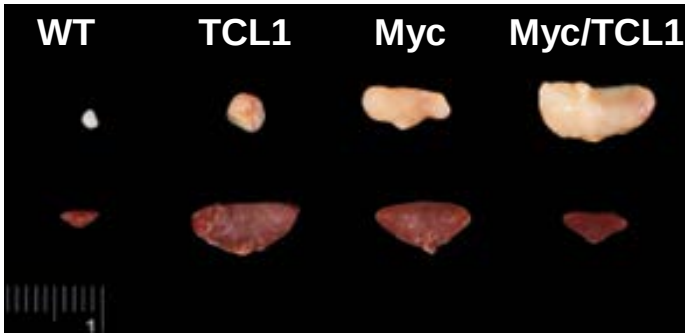
Eμ-Myc/TCL1 mouse model

- Eμ-Myc mouse overexpresses murine *c-Myc* under the MYC promoter and Ig_H Eμ enhancer Harris, AW et al *J Exp Med* (1988)
- Eμ-Myc x Eμ-TCL1 rapidly develops both a leukemia and lymphoma phenotype Rogers, KA et al *ASH* (2015)





Rogers, KA and Woyach, JA et al; Poster # 2752

12/6/2105 from 6 - 8 pm at Hall A, Level 2

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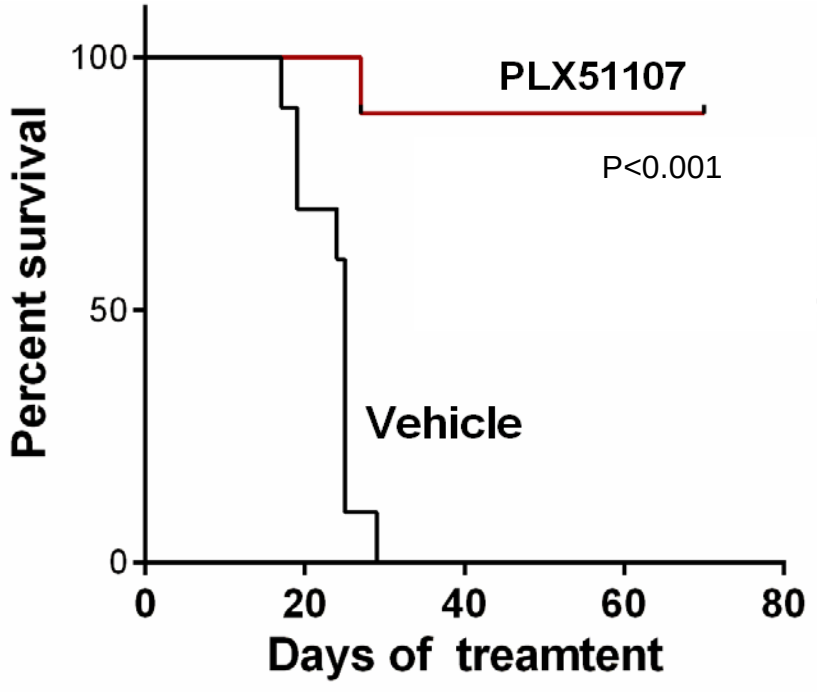
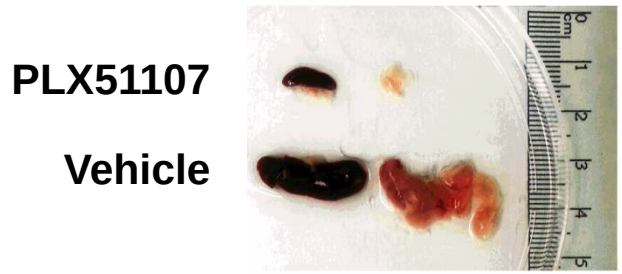
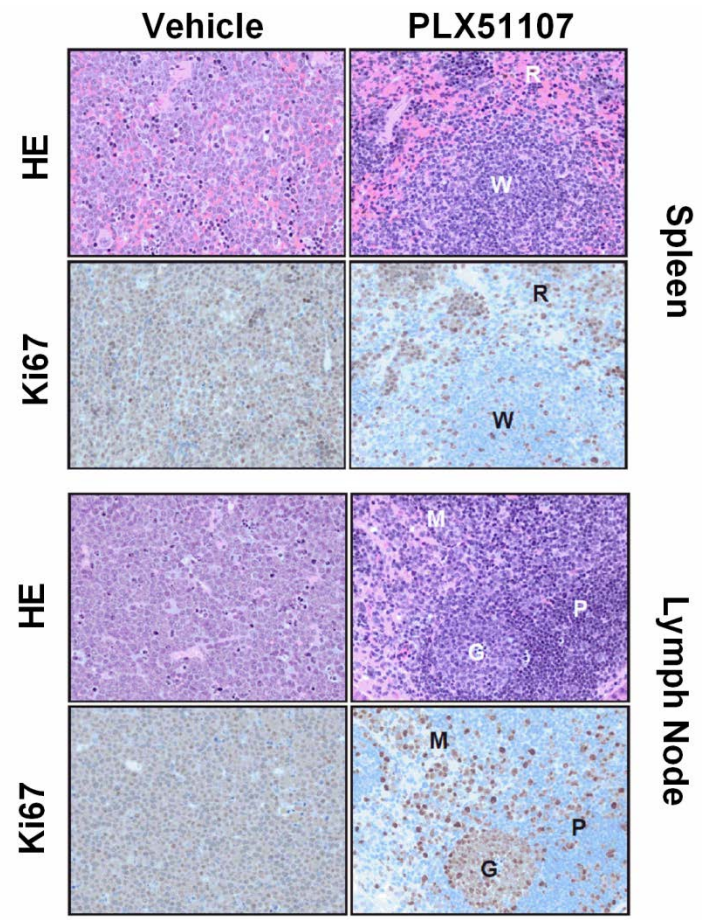
Anti-tumor effects of PLX51107 in Eμ-cMyc/TCL1 adoptive transfer model







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Conclusions

- BRD4 is a validated target in CLL
- BRD4 regulates known oncogenic drivers of CLL
- BRD4 inhibition can target multiple oncogenic pathways in CLL, thus serves as a potential therapeutic strategy
- PLX51107, a novel BET inhibitor, demonstrates potent *in vivo* anti-tumor activity

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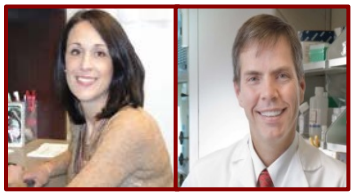

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