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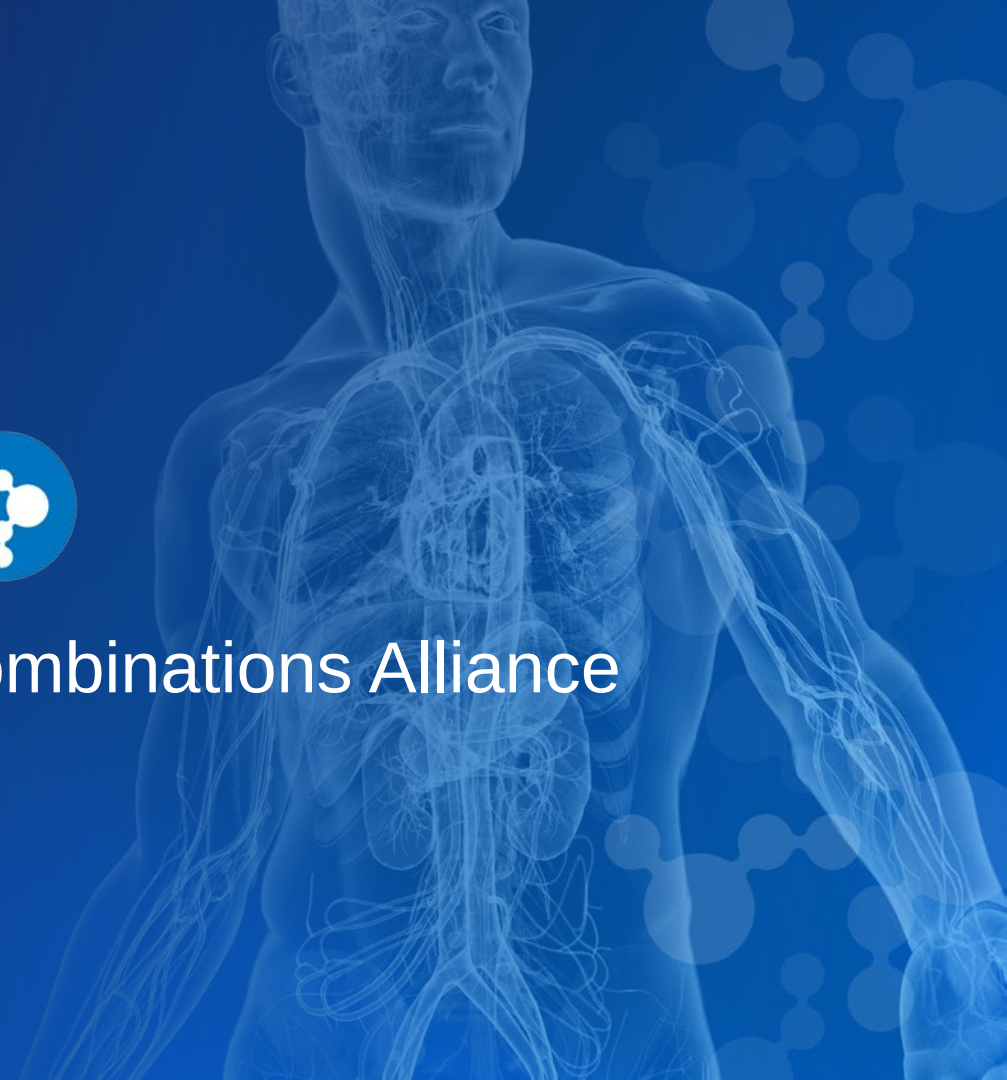
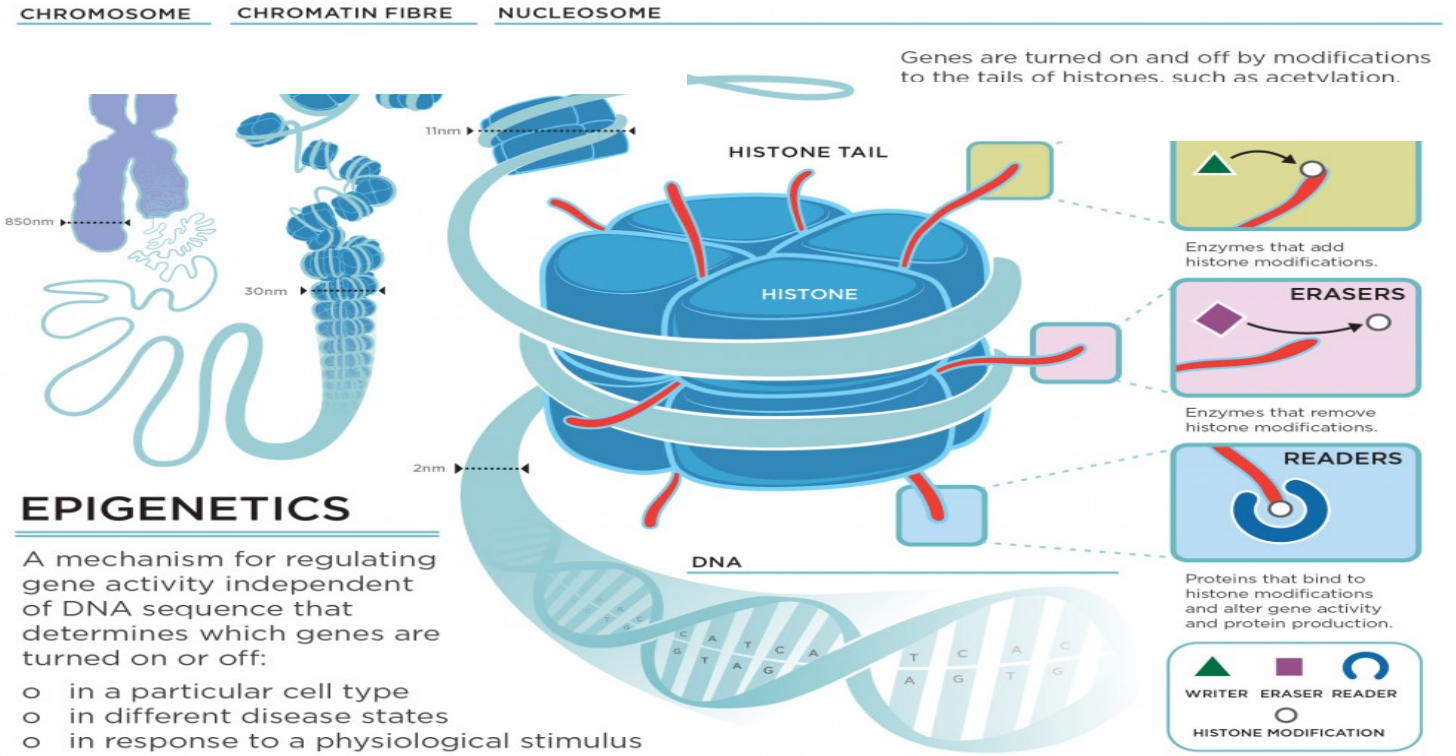
PLX51107 for CRUK Combinations Alliance

OCTOBER 2017



Epigenetic Regulation:
New Frontier for Drug Discovery
Enzymes & Protein interaction domains



- MTs (60)
- HATs (18)
- KDM (25)
- HDACs (11)
- SIRTs (7)
- M(K/R) (95)
- BRDs (46)

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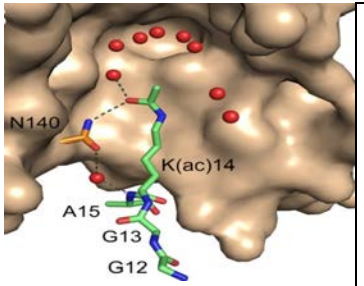
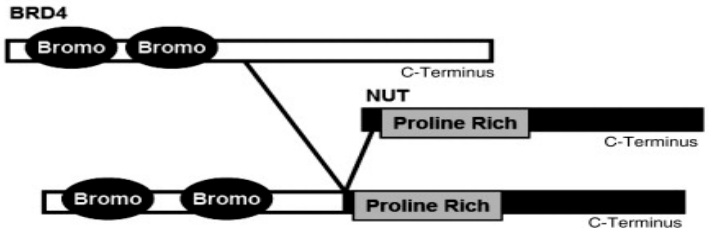
BET Protein Family
(Bromodomain and Extra-Terminal domain protein family)

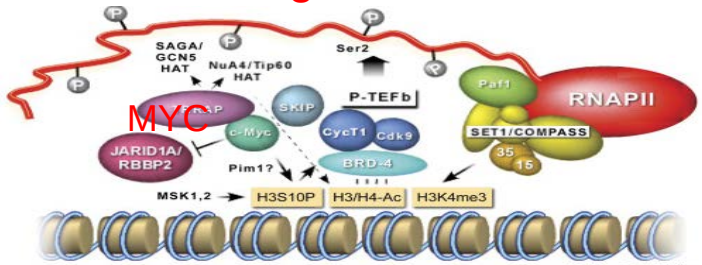


- Bromodomains ‘read’ acetylated lysines on histones
- The BET family includes BRD2, BRD3, BRD4 and BRDt
  - Diverse therapeutic potential: *initial validation in Oncology*
- Key mediators of transcriptional elongation
- Regulate activity of oncogenes (e.g. MYC) and oncogene fusions (e.g. NUT/NMC and MLL-fusions/AML)

Genetic rearrangement



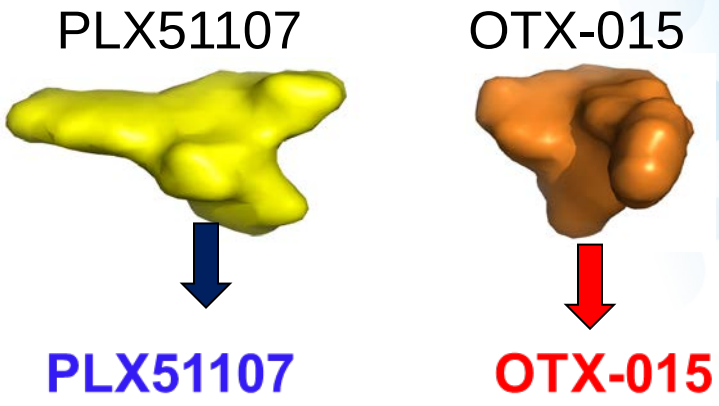
MYC oncogene

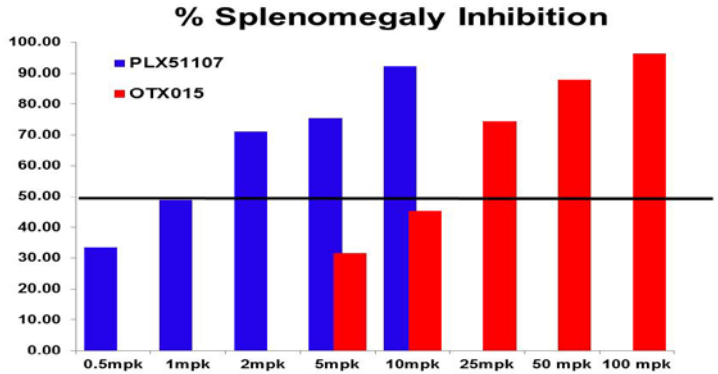


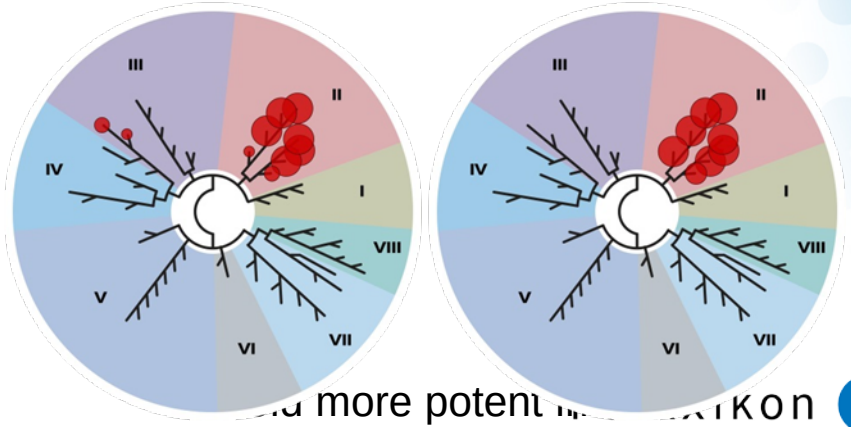
Current Opinion in Cell Biology

Discovery and Properties of PLX51107

In vitro Assay Data (IC_{50} nM)		
	PLX51107	OTX-015
BRD4(1,2) binding	20	50
MYC reporter assay	130	170
MV4-11 Proliferation	60	50
OCI-LY3 Proliferation	400	800





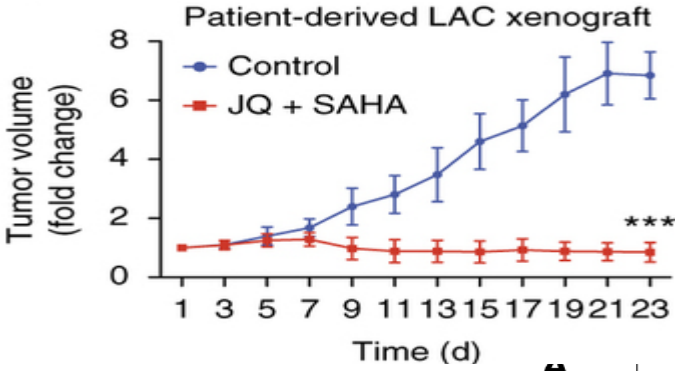


more potent

PLX51107 - Rationale for Collaboration with Combinations Alliance

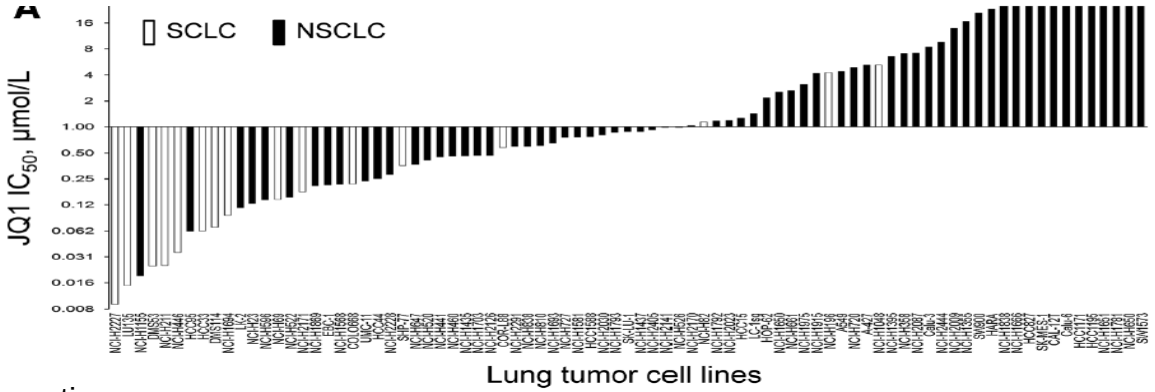
- Due to its therapeutic window, PLX51107 may be the most combinable BET inhibitor in clinical development
- Plexxikon is developing PLX51107 primarily for the treatment of hematologic malignancies
- Role of epigenetic regulation and gene expression presents combination opportunities in all cancers:
  - Immunotherapy
  - Targeted therapy
  - Chemo/Radiation
- Status: Dose escalation in solid tumors ongoing; dose escalation in hematologic malignancies to begin in December 2017

Sensitivity of lung cancer cell lines to targeted inhibition of BRD4



in vitro and *in vivo* activity of BRD4 inhibitors

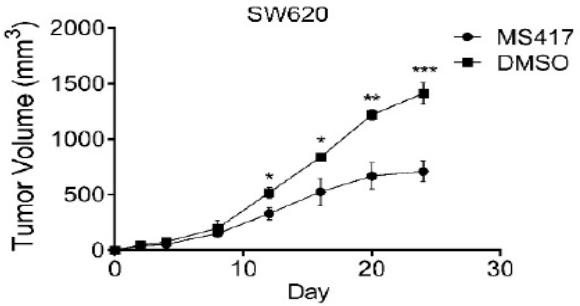
SCLC appears more sensitive than NSCLC



Lenhart et al 2015, Mol Cancer Therapeutics

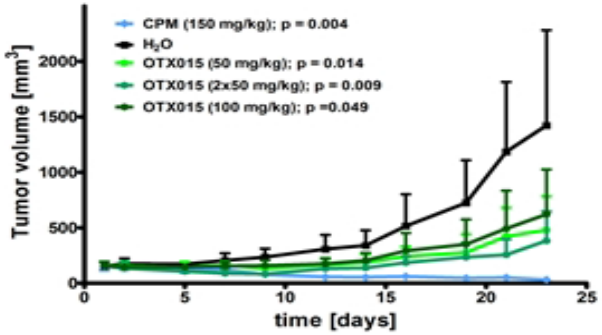
Sensitivity of solid tumors to targeted inhibition of BRD4

CRC



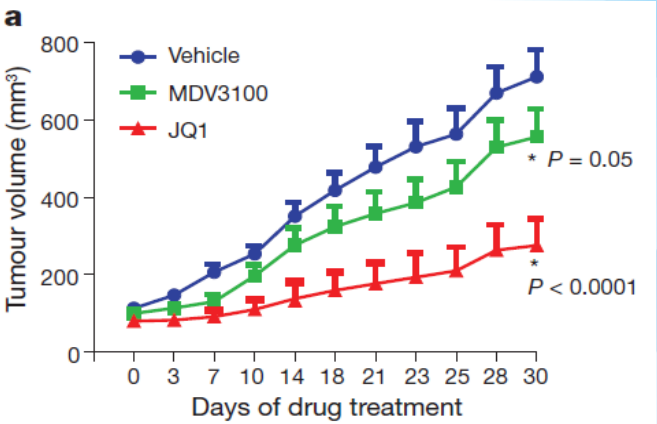
Yuan Hu, Int. J. Mol. Sci. 2015

Neuroblastoma



(Poster Presentation OncoEthix)

Prostate



Asangani, Nature, 2014

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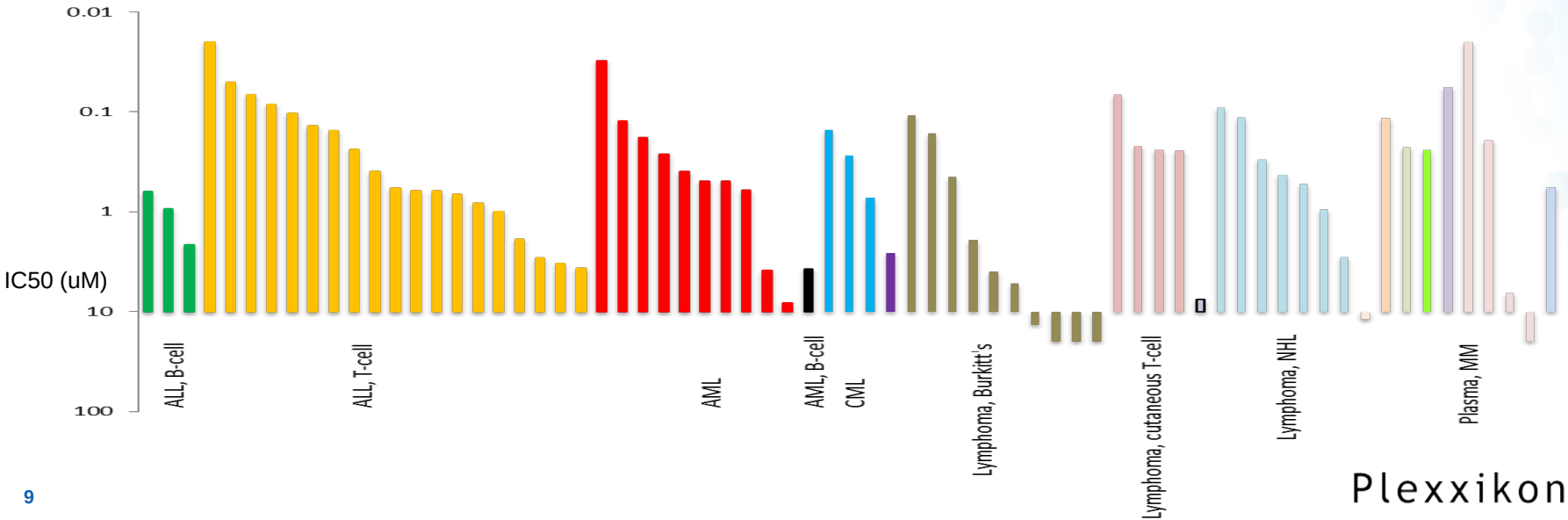
PLX51107 Exhibits Broad Activity in Hematological Malignancies

- Submicromolar activity against most leukemia & lymphoma cell lines
- Selective killing of tumor cells in multiple in vivo models



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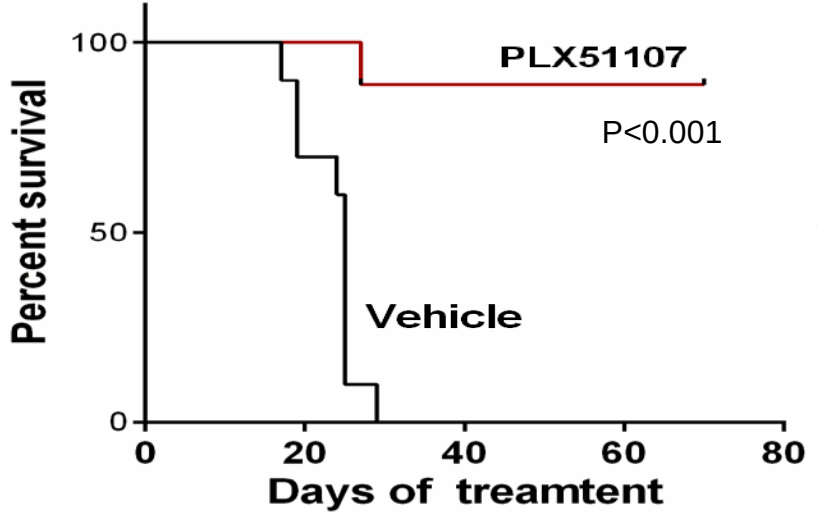
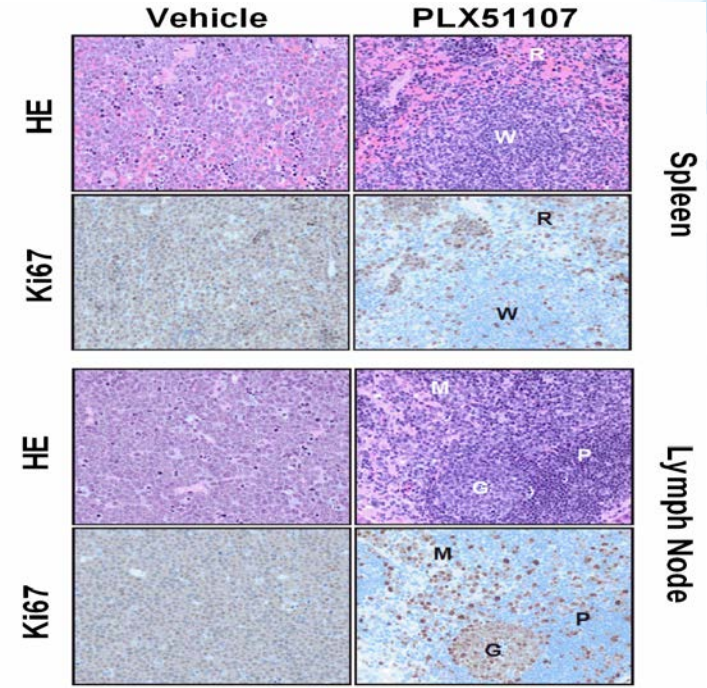
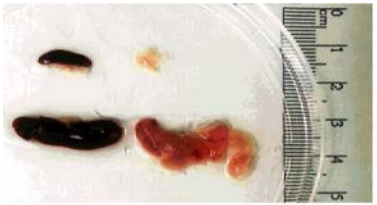
Anti-tumor effects of PLX51107 in Eμ-cMyc/TCL1 adoptive transfer model of CLL





PLX51107

Vehicle



Data from Rosa Lapalombella, John Byrd, and colleagues

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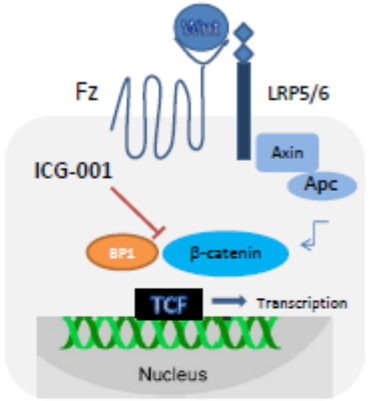
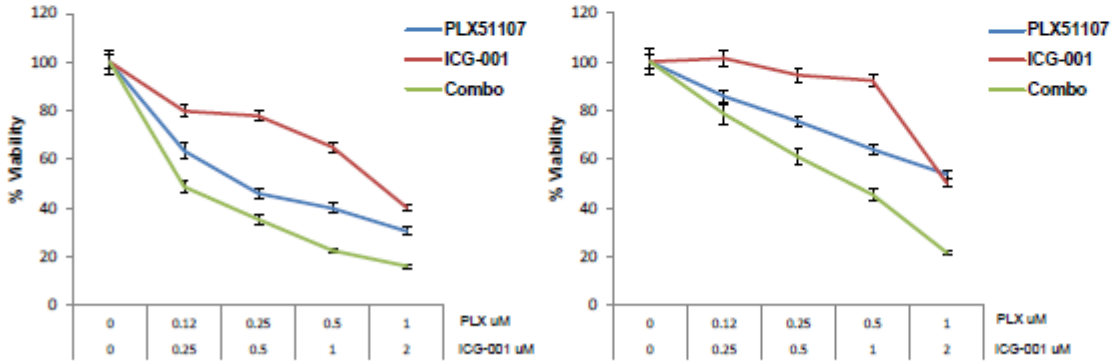
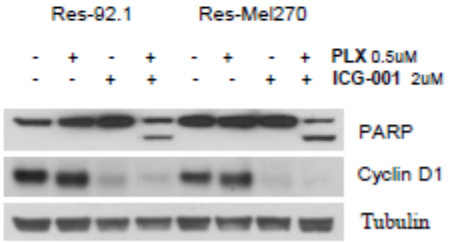
Synergy of PLX51107 + ß-catenin inhibitor in uveal melanoma cells

A. Combination **PLX51107 + ICG-001** (inhibitor of β-catenin/BP1 binding)

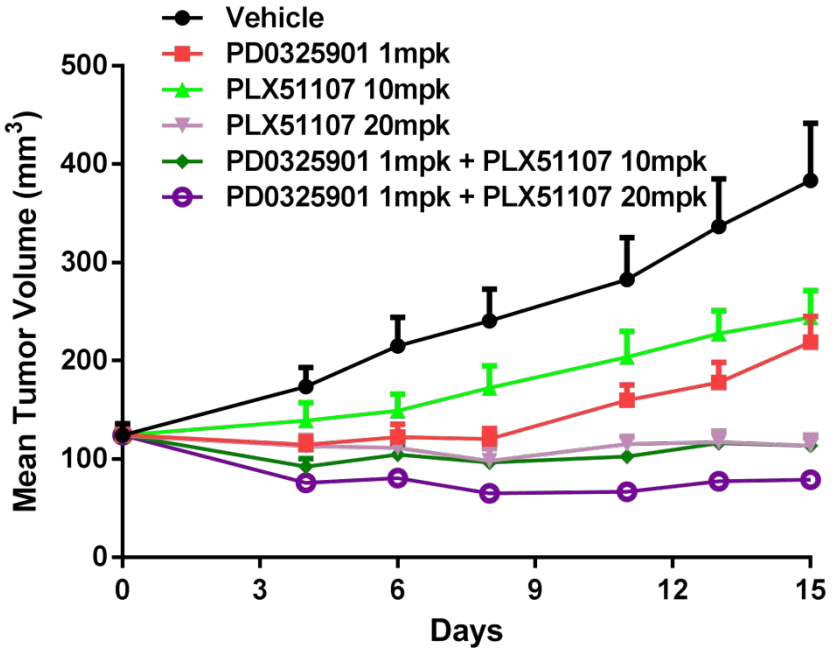


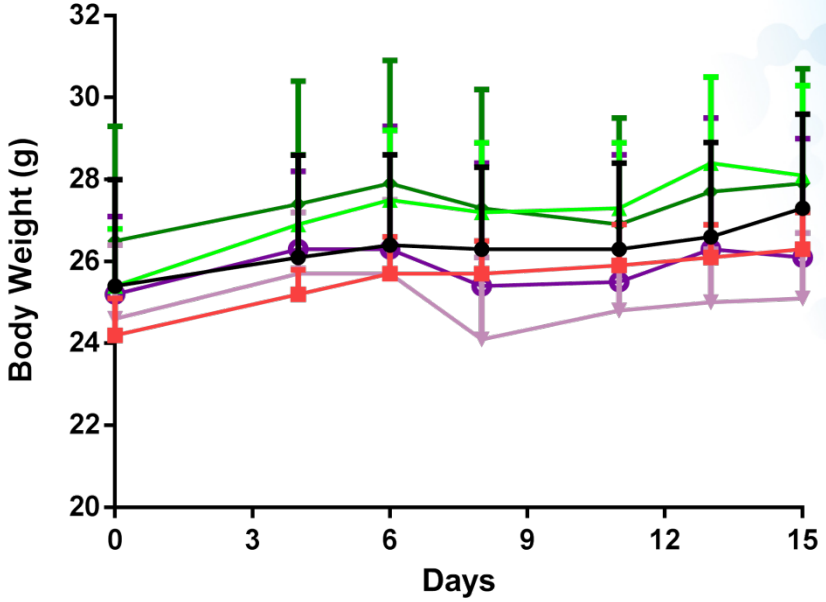
Synergy: Combination Index < 1





PLX51107 + MEK Inhibitor Combinations Suppress IPC298 Growth *in vivo*





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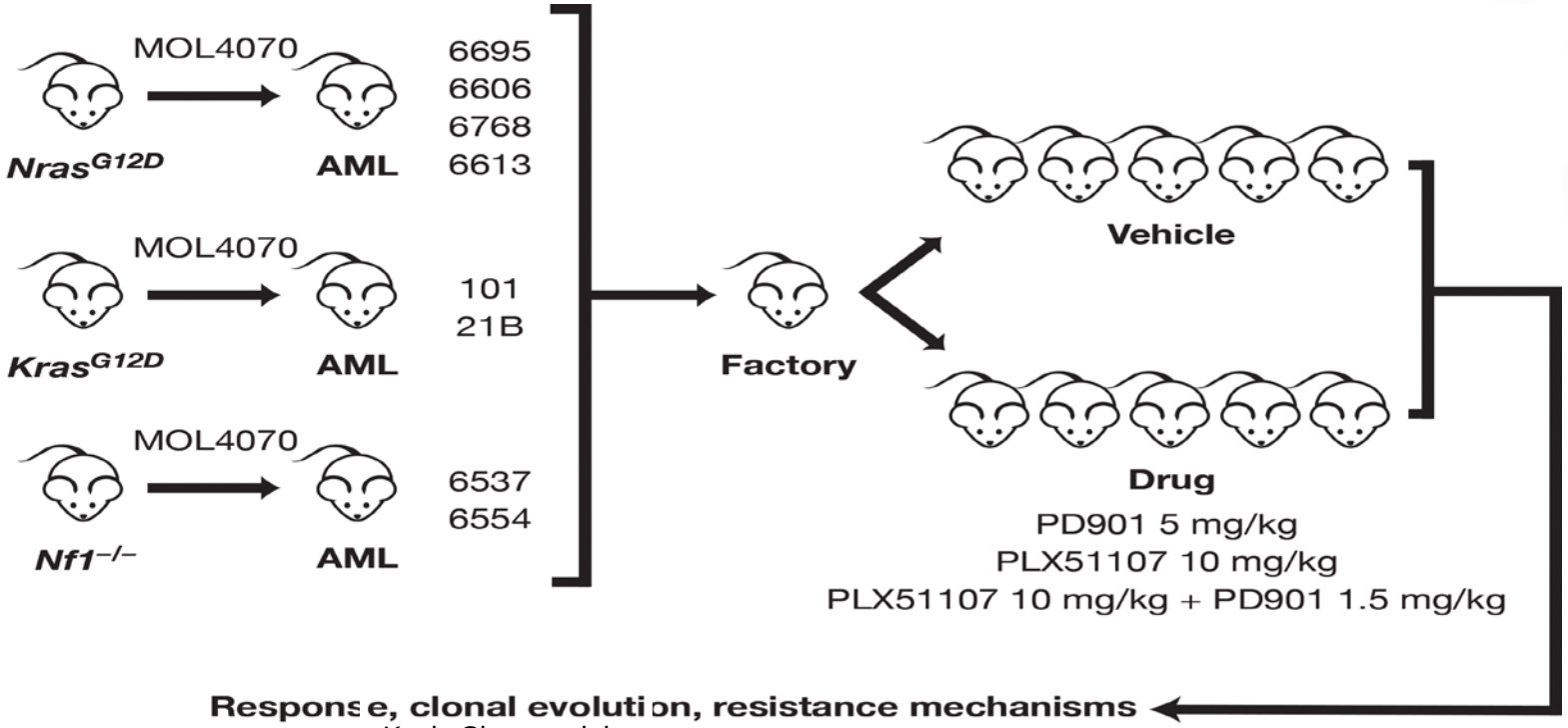
Combination Activity of PLX51107 and MEK inhibitor in AML Models



Kevin Shannon lab,
UCSF

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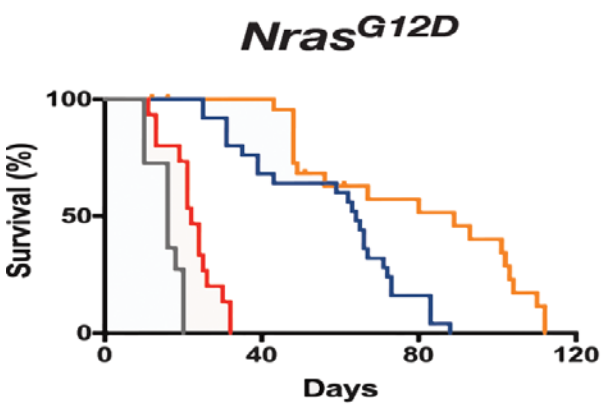
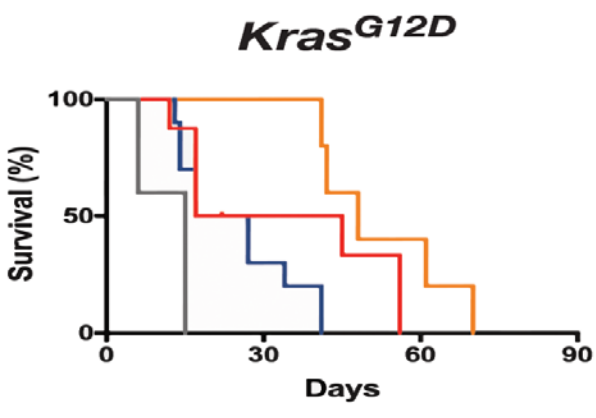
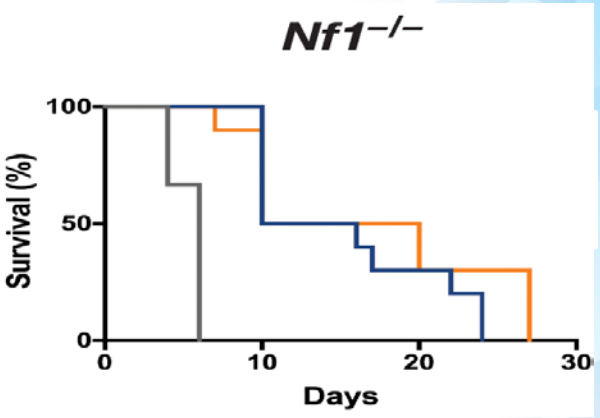
Comparative efficacy of PLX51107 + MEKi on $Nras^{G12D}$, $Kras^{G12D}$, and $Nf1^{-/-}$ AMLs



4 Models



2 Models



2 Models

Vehicle
(MEKi) PD901
(BETi) PLX51107
(Combo) PLX51107+PD901

Kevin Shannon lab, UCSF

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PLX51107 Clinical Development Plan
Single agent explorations

Arm	Population
Phase 1 Dose Escalation	
Group A	Any advanced solid tumor, including lymphomas - Ongoing
Group B	R/R AML, high-risk MDS - Set to begin in December 2017
Phase 2 Dose Expansion	
	Assorted Myeloid malignancies
	Assorted Lymphoid malignancies

PLX51107 Combinations Alliance

- Plexxikon is soliciting proposals for rational combinations in patient populations with unmet medical need
- Further information is available under CDA
- Questions? Please contact us:
  - Marguerite Hutchinson, Sr. Director, Business Development: mhutchinson@plexxikon.com