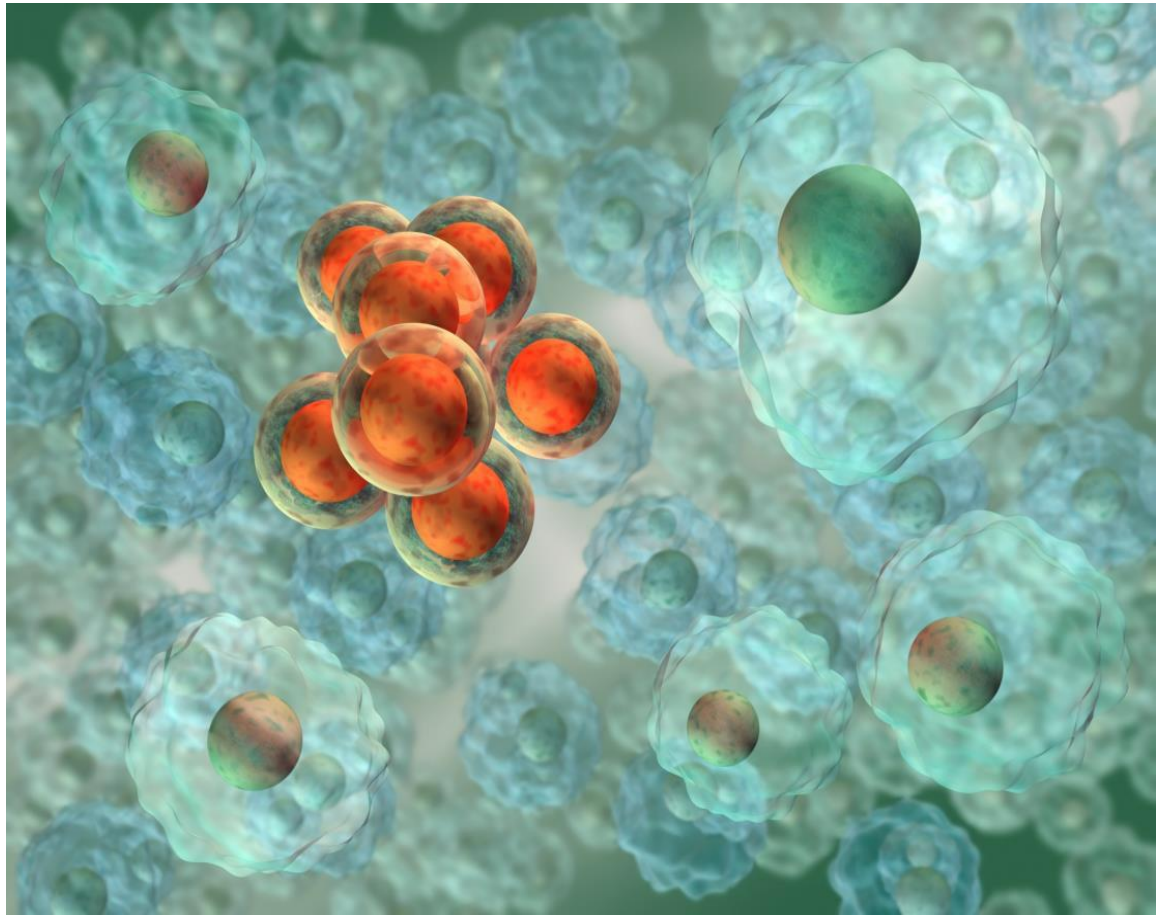
ZENITH EPIGENETICS

Developing Best in Class BET Inhibitors for Oncology & AI: from Discovery to the Clinic



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EpiCongress July 2014

Zenith Epigenetics Overview

Formed from Resverlogix as an independent company to develop a novel epigenetic platform for oncology and autoimmune diseases

- **Developing small molecule inhibitors against BET Bromodomains (BET)**

Clinical studies initiating with ZEN-3365 in 2H 2014
for hematological malignancies & 1H 2015 for solid tumors

- **Strong PD and efficacy effect in multiple *in vitro* and *in vivo* models**
- **Molecularly defined patient subsets for development in AML, DLBCL, and other hematological and solid tumor indications**

Broad chemistry platform and IP estate

In vivo Proof of Concept in multiple models of autoimmune disorders

Phase I BET Inhibitor Oncology Clinical Trials
Activity shown with OTX-015

ZENITH EPIGENETICS

Company	Drug	Indications
Zenith Epigenetics	ZEN-3365	AML, LPD
Zenith Epigenetics	ZEN-3365	Solid
GlaxoSmithKline	I-BET762	NUT midline carcinoma and other solid tumors
GlaxoSmithKline	I-BET762	Relapsed, Refractory Hematologic Malignancies
Constellation Pharmaceuticals	CPI-0610	Progressive lymphomas
Constellation Pharmaceuticals	CPI-0610	Multiple myeloma
Constellation Pharmaceuticals	CPI-0610	AML, ALL, acute undifferentiated or biphenotypic leukemia, CML in blast crisis, MDS or MDS/MPN
Tensha Therapeutics	TEN-010	Advanced solid tumors, NUT midline carcinoma
OncoEthix	OTX015	Haematological Malignancies • Efficacy in lymphoma & AML below MTD

Zenith's broad platform has generated high potency BETi with desirable pharmaceutical properties

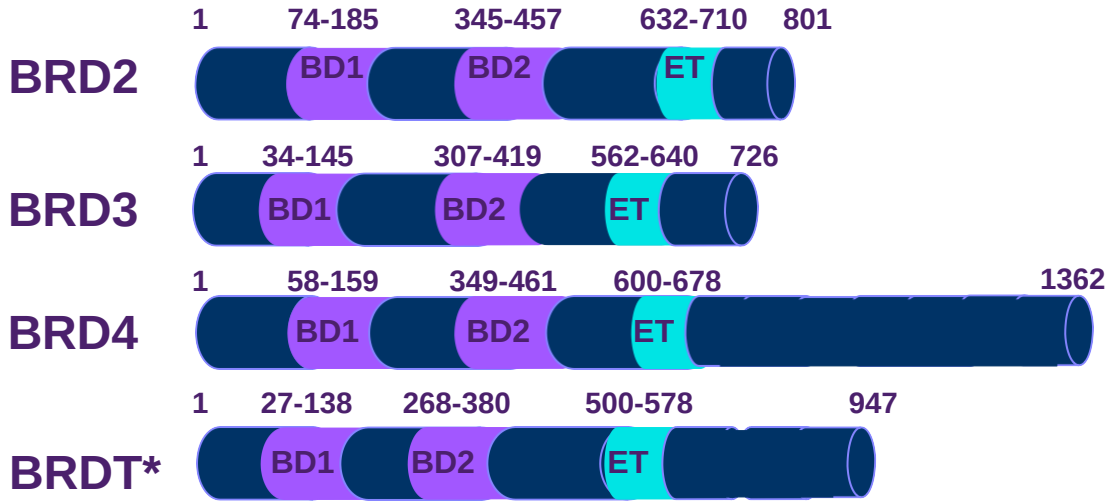
ZEN-3365 selected as Development Candidate from a panel of excellent compounds

Compound ID	FRET Brd4(1) IC50 (uM)	FRET Brd4(12) IC50 (uM)	c-MYC IC50 (uM)	Proliferation IC50 (uM)	PK (Rat)	In Vivo Efficacy MV4-11 Xenograft
ZEN-3365	0.04	0.05	0.09	0.10	+++	✓
ZEN-3309	0.05	0.05	0.46	0.79	+++	✓
ZEN-3293	0.07	0.12	0.61	0.84	+++	✓

- **Novel scaffolds generated by virtual screening → SAR**
- **Favorable Chemical Properties**
  - Chemically distinct from known BET inhibitors
  - Tractable SAR, chemistry allows for fast library synthesis and scale-up, >1300 compounds synthesized
- **Good Pharmaceutical Properties for Lead Molecules**
  - Good solubility across pH; High permeability (Caco-2 assay; oral absorption)
  - Good oral bioavailability
- **Strong IP portfolio of novel scaffold – diverse from other BET inhibitors in development**

ZEN-3365 selectively binds BET bromodomains

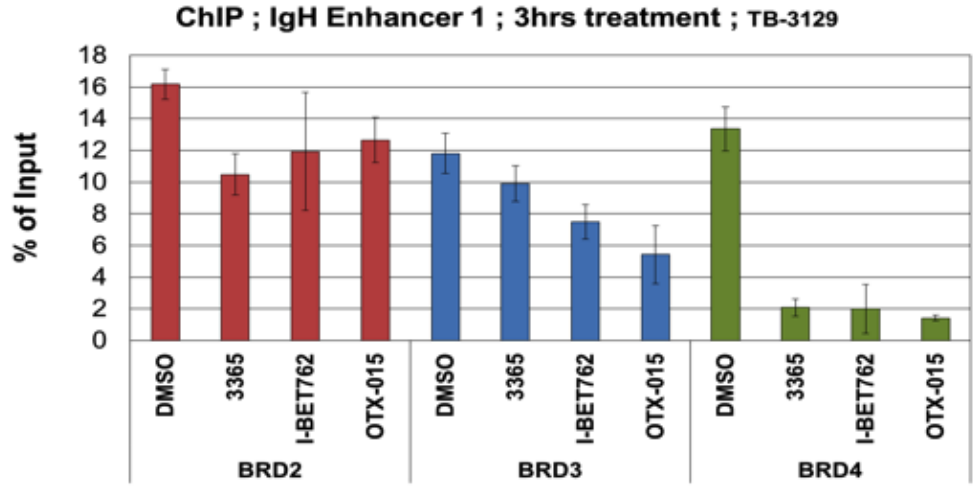
- 10 – 40 nM IC50 for BET bromodomains
- > 20-fold selectivity for BRD4(1) vs non-BET bromodomains
- > 200-fold selectivity vs 68 cellular receptors
- 0/456 kinase domains bound

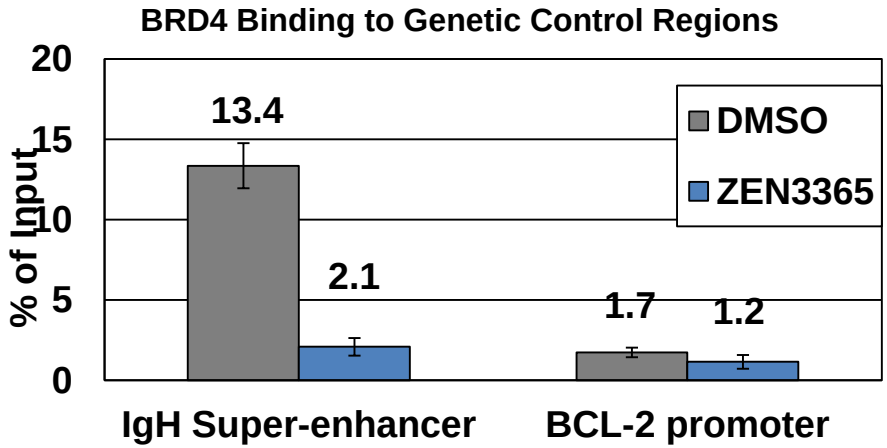


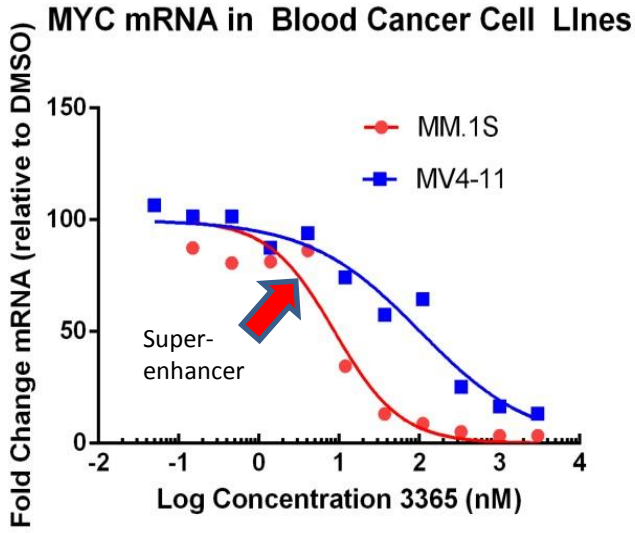
	ALPHAScreen IC50 (uM)										
Compound	BRD2 (1)	BRD2 (2)	BRD2 (1,2)	BRD3 (1)	BRD3 (2)	BRD3 (1,2)	**BRD4 (1)**	BRD4 (2)	BRD4 (1,2)	BRDT (1)	BRDT (1,2)
JQ1	0.08	0.05	0.03	0.04	0.03	0.02	**0.06**	0.04	0.05	0.15	0.13
I-BET762	0.06	0.01	0.02	0.02	0.02	0.05	**0.04**	0.01	0.03	0.12	0.11
ZEN-3365	0.03	0.01	0.02	0.01	0.01	0.01	**0.02**	0.01	0.04	0.10	0.04

ZEN-3365 selectively displaces BRD4 from a super-enhancer to selectively repress gene expression

- ZEN-3365 more potently represses super-enhancer driven *MYC* expression in MM.1S than regular enhancer/promoter driven BCL-2 in MM.1S or regular promoter-driven *MYC* in MV4-11 cells

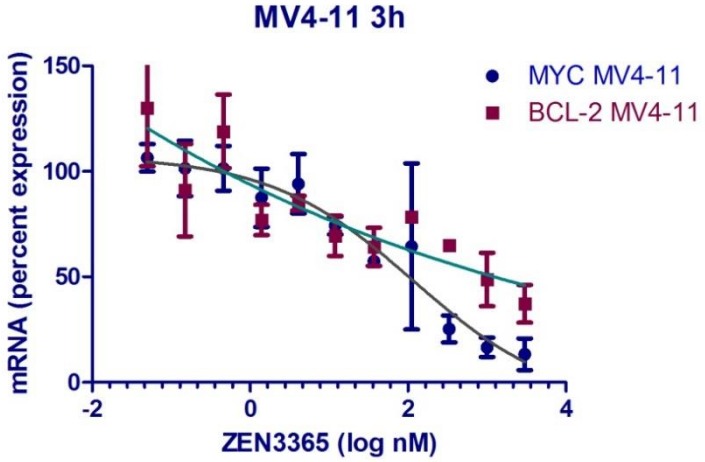


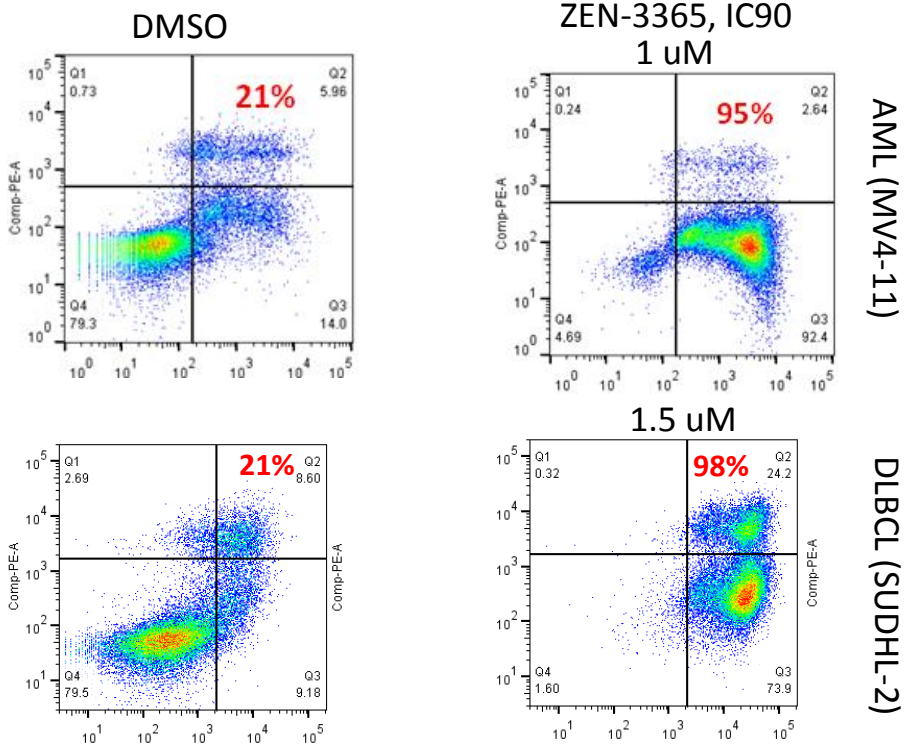




ZEN-3365 inhibits expression of MYC and BCL-2 and induces apoptosis in AML and DLBCL

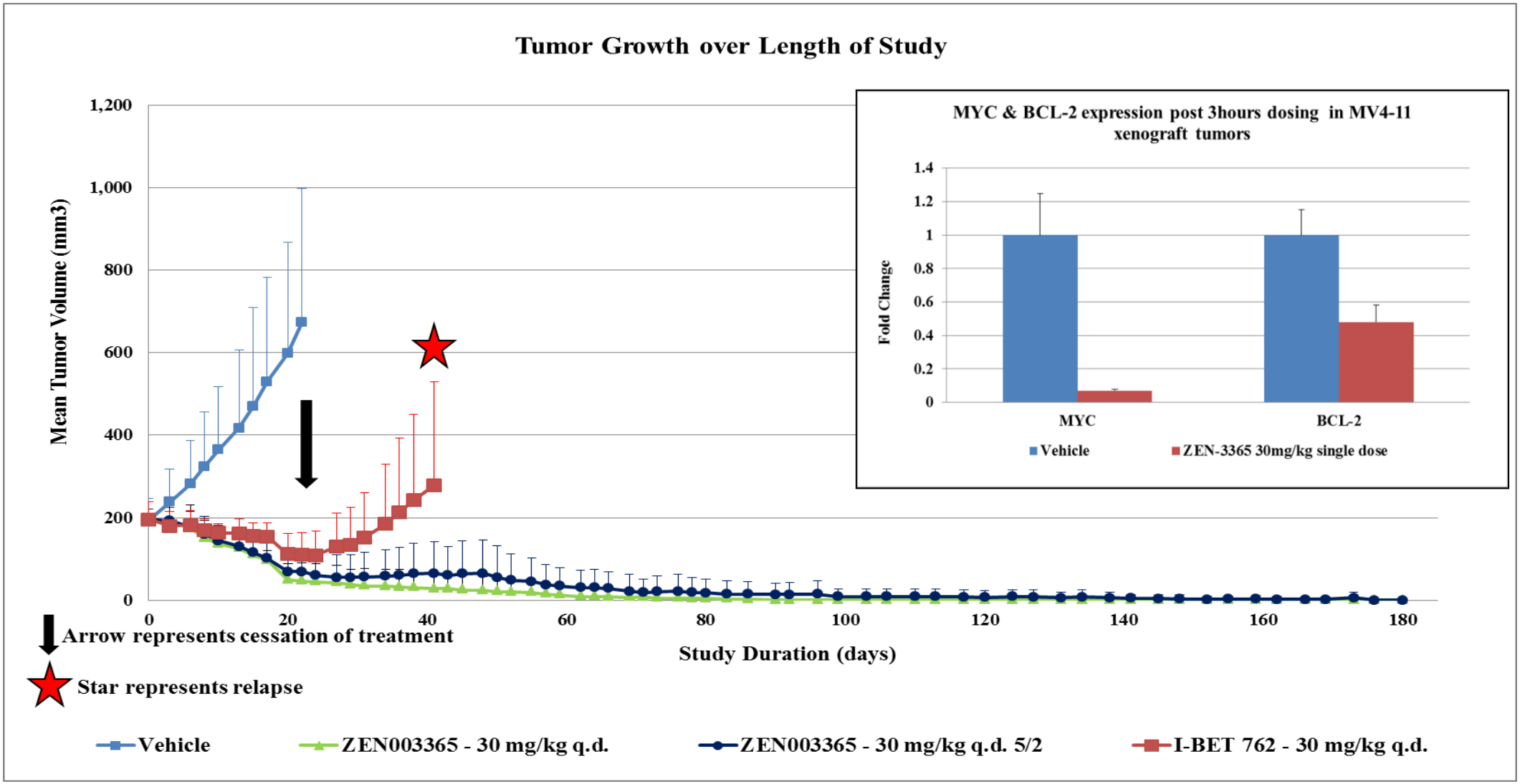
mRNA	IC50 (nM) MV4-11	IC50 (nM) SUDHL-2	IC50 (nM) SUDHL-4
MYC	90	91	176
BCL-2	120	97	140





- **ZEN-3365 reduces expression of MYC & BCL-2 mRNA and protein in AML & DLBCL cell lines**
- **Drives cell cycle arrest, apoptosis**

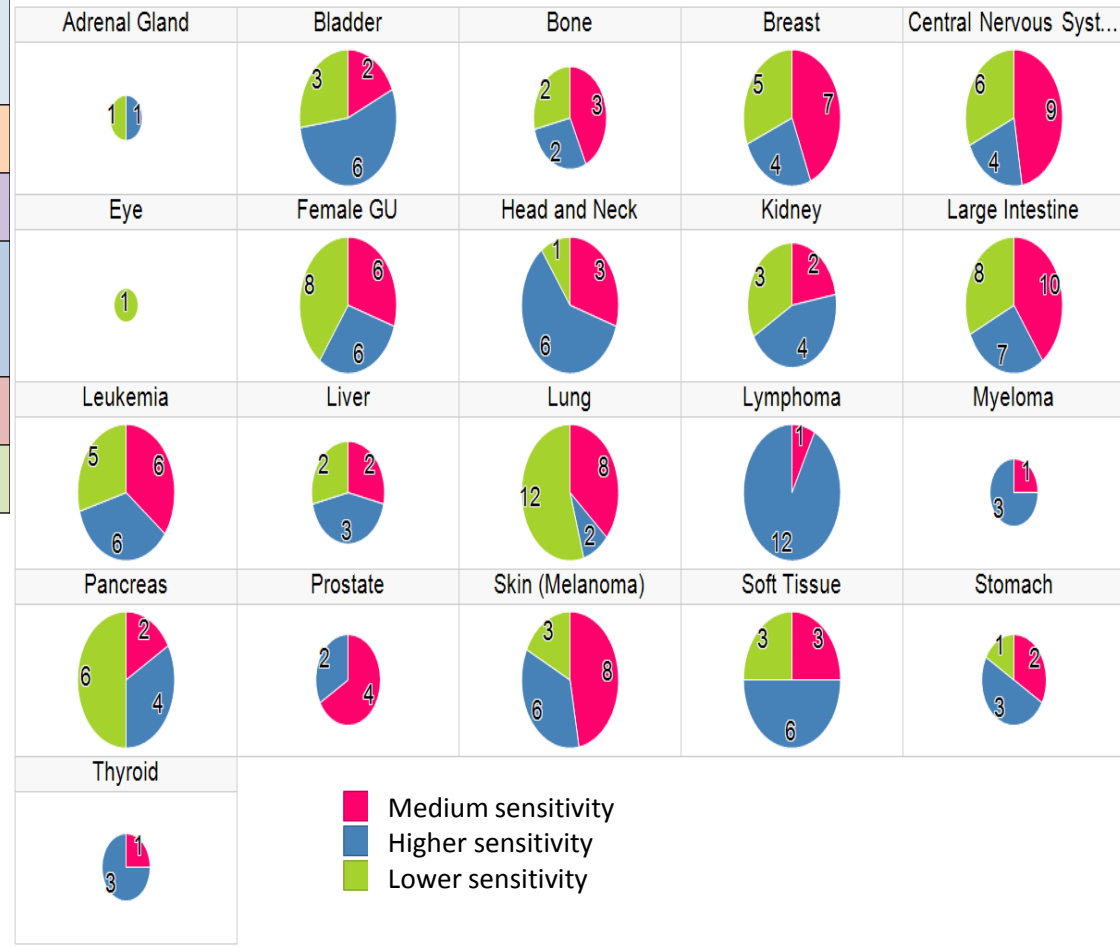
MV4-11 xenograft model: ZEN-3365 causes durable tumor regression



ZEN-3365 potently inhibits proliferation of solid tumor cell lines

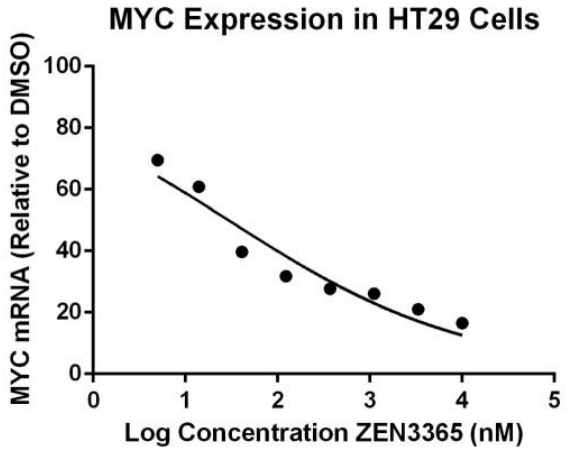
Cell Line	Tumor Type	IC50 (uM)
MDA MB 231	Breast	0.37
HT-29	Colon	0.54
SCC-9	Head and Neck	0.32
DMS273	Lung	0.38
BPH1	Prostate	0.31

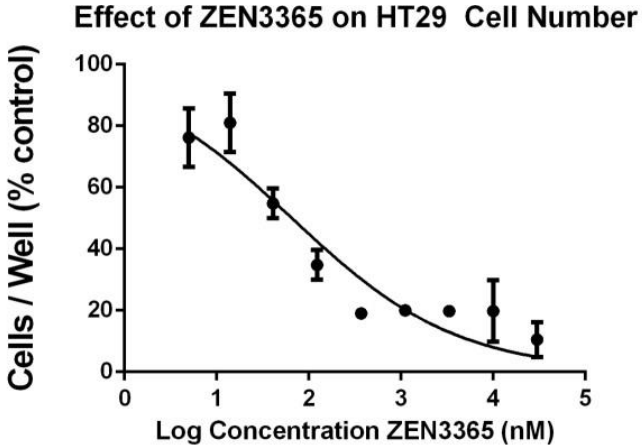
Tumor type	No. cell lines	No. IC50 < 2 uM
CRC	23	15
CRPC	6	4
Breast	16	10
H & N	8	8

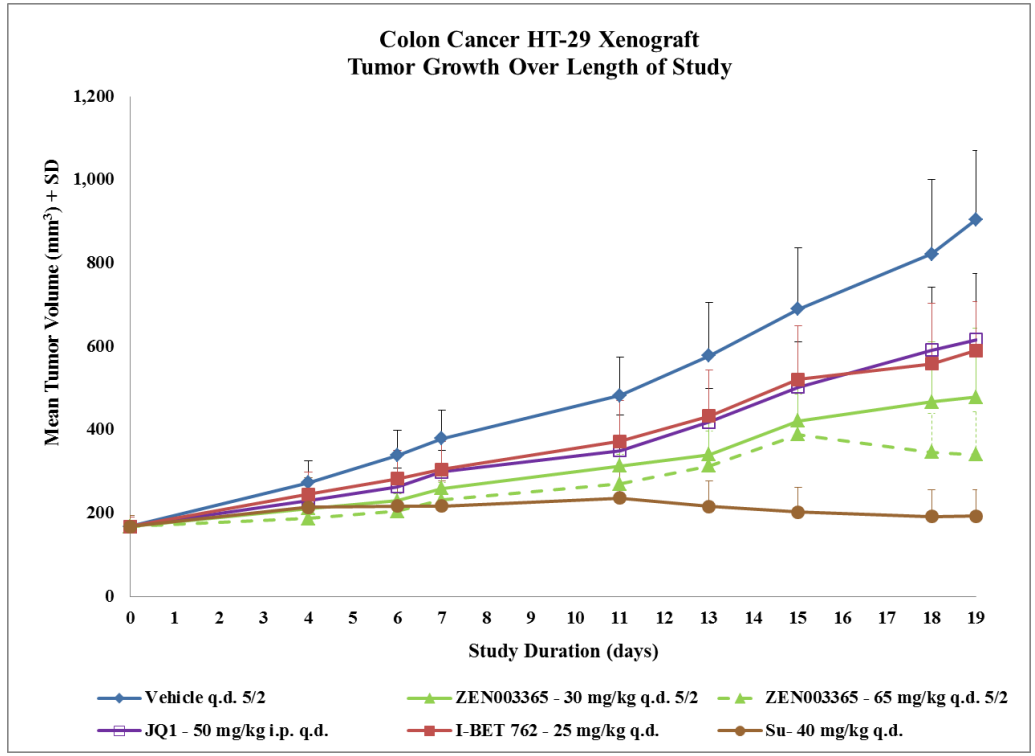


ZEN-3365 inhibits MYC expression & CRC proliferation in vitro and inhibits xenograft growth

- ZEN-3365 inhibits MYC expression and HT29 colorectal carcinoma cell proliferation (IC50 = 66 nM); is well-tolerated and see 58 – 77% TGI at 30 and 65 mg/kg q.d. 5/2







ZEN-3365 is a compelling molecule for clinical development

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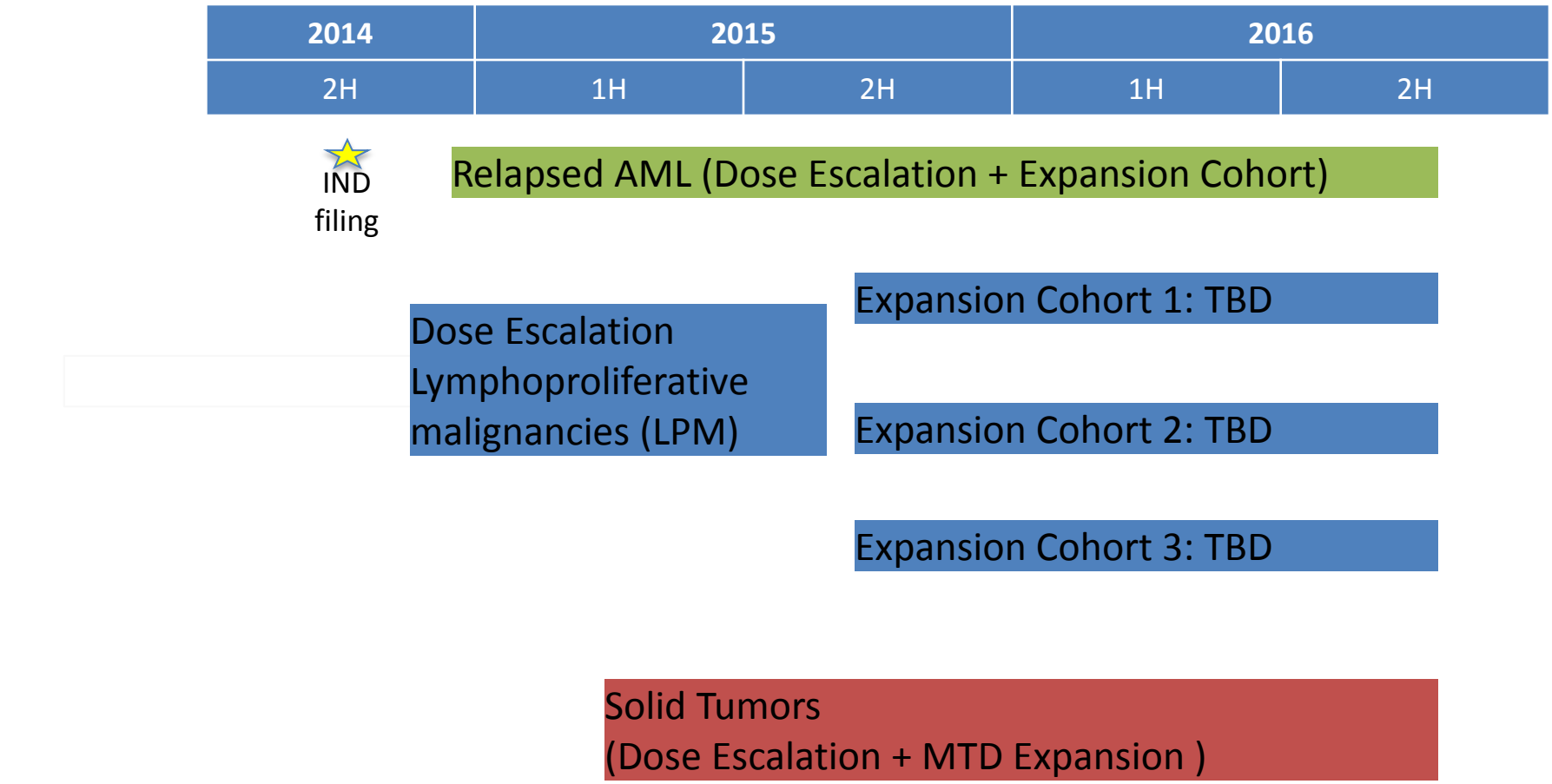
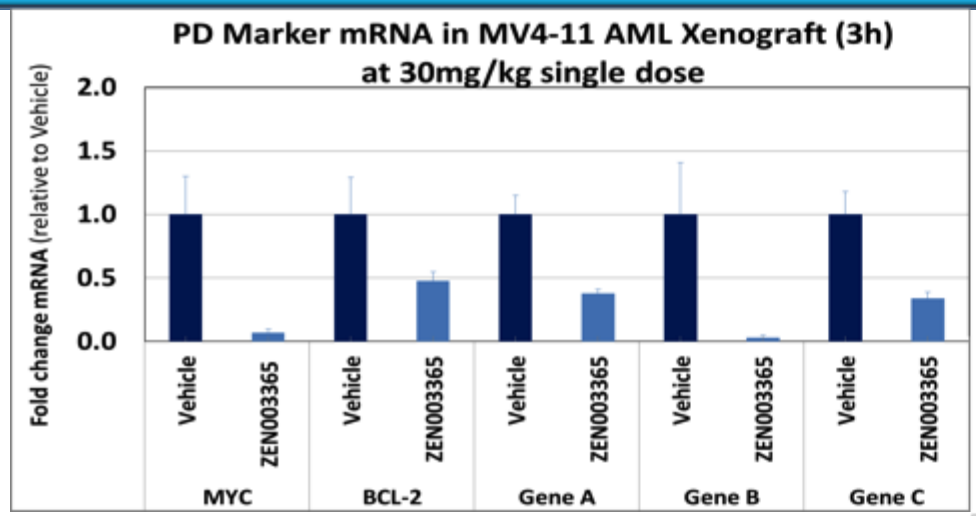
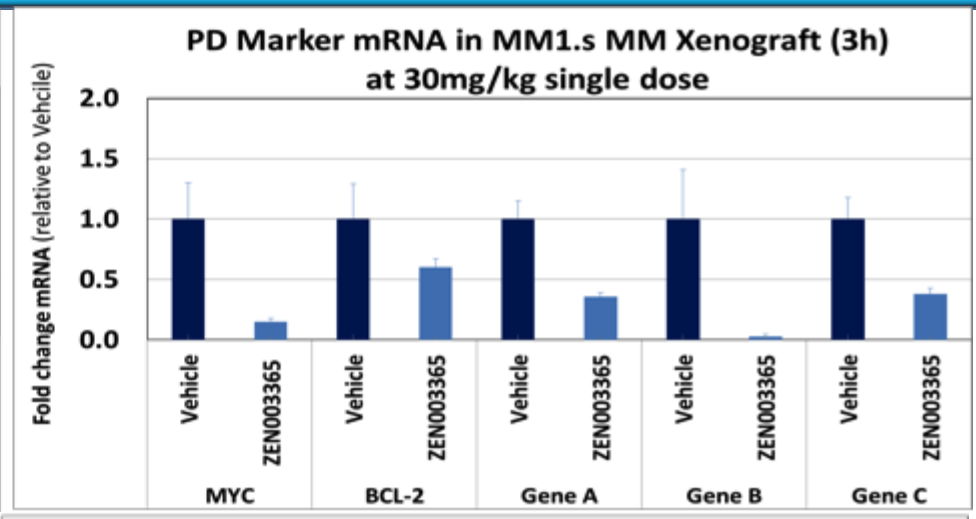
Feature	Comments
Potency	50 nM BRD4 ; 90 nM MYC ; 160 nM MV4-11 proliferation
Selectivity	Highly selective for BET proteins Does not inhibit kinases No off-target binding to Panlabs 68 receptor panel
PK/PD	Orally bioavailable, level and duration of exposure achieved for modulating target and effecting pharmacodynamics
Pre-clinical Efficacy	Active in multiple hematologic & solid tumor xenografts Active in AML patient derived primary cells Active in multiple hematologic solid tumor cell lines
Toxicity Profile	Reversible, manageable, and on target
Synthetic Route	3 linear high yielding GMP steps, no chromatography steps

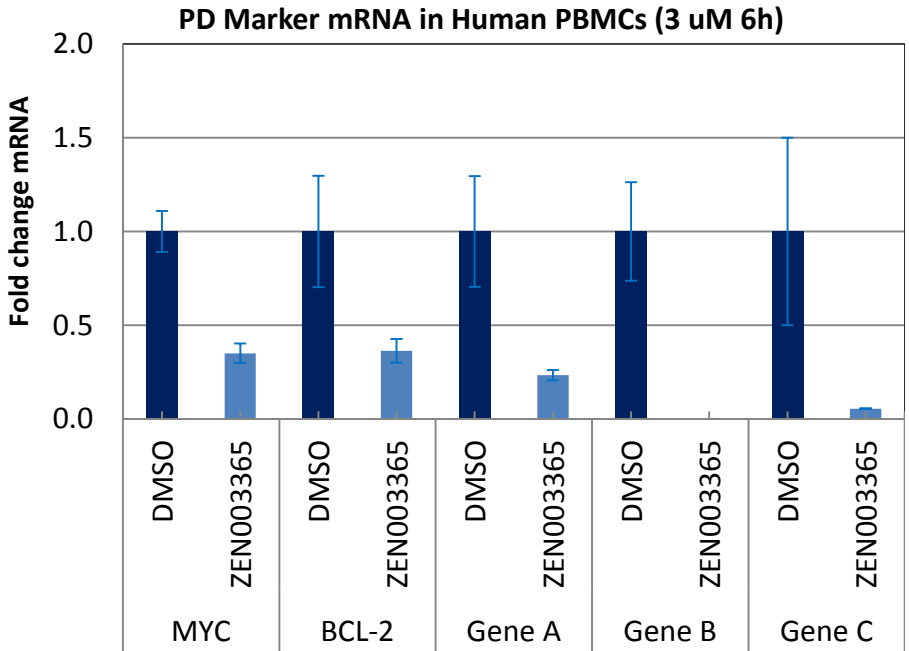
Phase 1 study of ZEN-3365: First patient in 3Q 2014

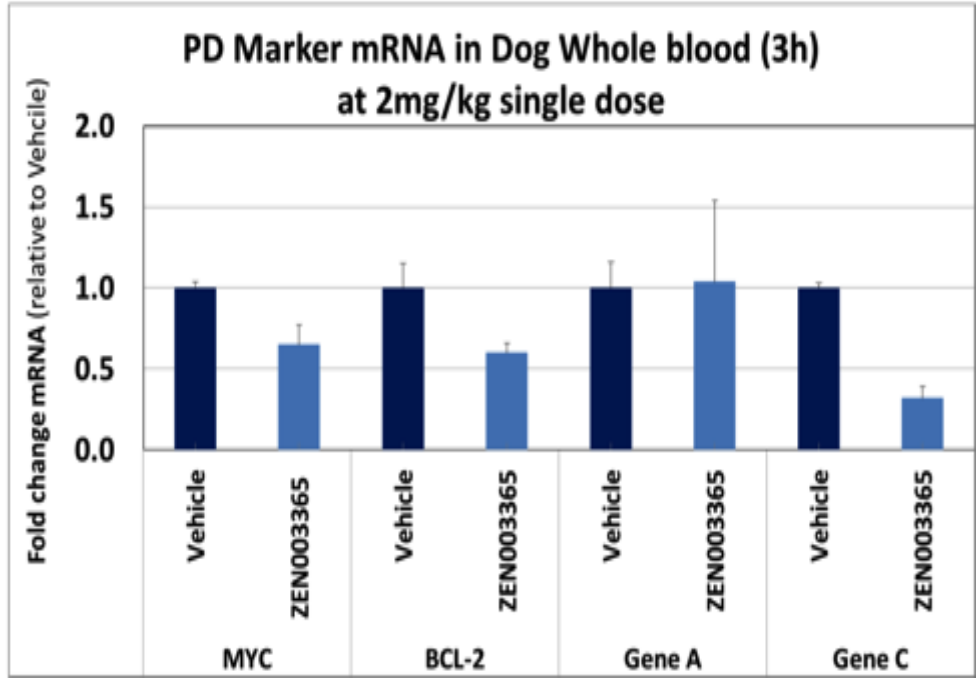


BETi gene signature will be used to evaluate PD in clinic









Zenith's biology selectivity platform: developing next generation BD1 selective compounds

Zenith's compounds can uniquely dissect BD1 vs BD2 biology

- Zenith has BD2 selective and pan-selective compounds
  - BD1 [BRD4 (1)] binding is necessary to inhibit *MYC* expression and proliferation; evaluating whether BD1 is sufficient
  - BD2 [BRD4(2)] binding is not sufficient

	Compound	BRD4(1) IC50 (uM)	BRD4(2) IC50 (uM)	MYC IC50 (uM)	Proliferation IC50 (uM)
BD2 Selective	ZEN222	3.0	0.06	8.5	14
	ZEN297	1.2	0.02	1.3	3.1
	ZEN2135	1.0	0.04	3.1	5.6
Pan Selective	ZEN3118	0.09	0.03	0.50	1.16
	ZEN3212	0.02	0.01	0.31	0.30
	ZEN3228	0.08	0.03	0.73	0.93
	ZEN3309	0.06	0.03	0.41	0.67
	ZEN3317	0.03	0.01	0.27	0.56
	ZEN3365	0.02	0.01	0.09	0.16

Zenith has irreversible BD1 selective tool compounds

- Tool to investigate BD1/BD2 selectivity question
- Covalent irreversible BD1 binding results in persistent inhibition of a subset of BETi regulated gene expression; tool to further dissect BET dependent gene regulation

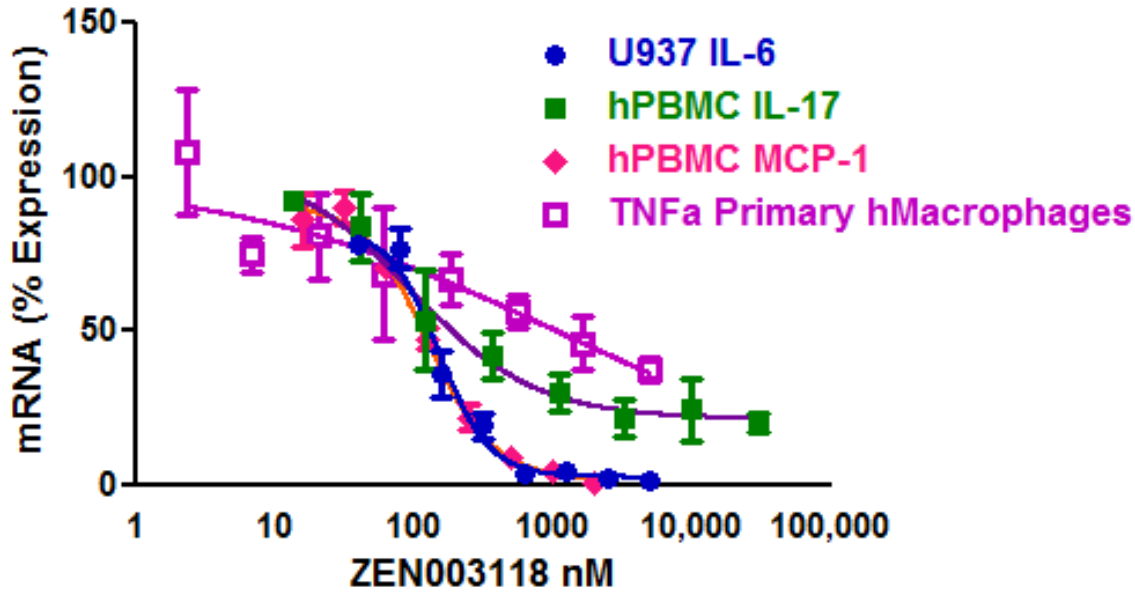
Zenith's robust platform has generated promising BET inhibitors for auto-immune disorders

Compound ID	FRET Brd4(1) IC50 (uM)	FRET Brd4(12) IC50 (uM)	IL6 IC50 (uM)	IL17 IC50 (uM)	PK (Rat)	In Vivo Efficacy
ZEN-3118	**0.07**	**0.07**	**0.23**	**0.19**	+++	Rat CIA Mouse EAE
ZEN-3309	0.05	0.05	0.23	0.36	+++	Rat CIA
ZEN-3228	0.03	0.03	0.54	0.26	+++	Mouse EAE
ZEN-3212	0.03	0.06	0.13	0.15	+++	Mouse EAE

- Separate IP space than ZEN-3365 and oncology molecules
- Potent BRD4 inhibitors with good drug like properties
- Inhibits auto-immune-related gene expression in vitro
- Efficacious in multiple auto-immune in vivo models
- Well tolerated at efficacious doses

ZEN-3118 inhibits human autoimmune-related gene expression in vitro

- Zenith has demonstrated multiple cell systems where BETi inhibit drivers of autoimmune disease (antigen stimulation of T cells; macrophages; synovial fibroblasts)
- IL-6, TNFa and IL-17 are implicated in rheumatoid arthritis
- IL-17 and MCP-1 are implicated in multiple sclerosis

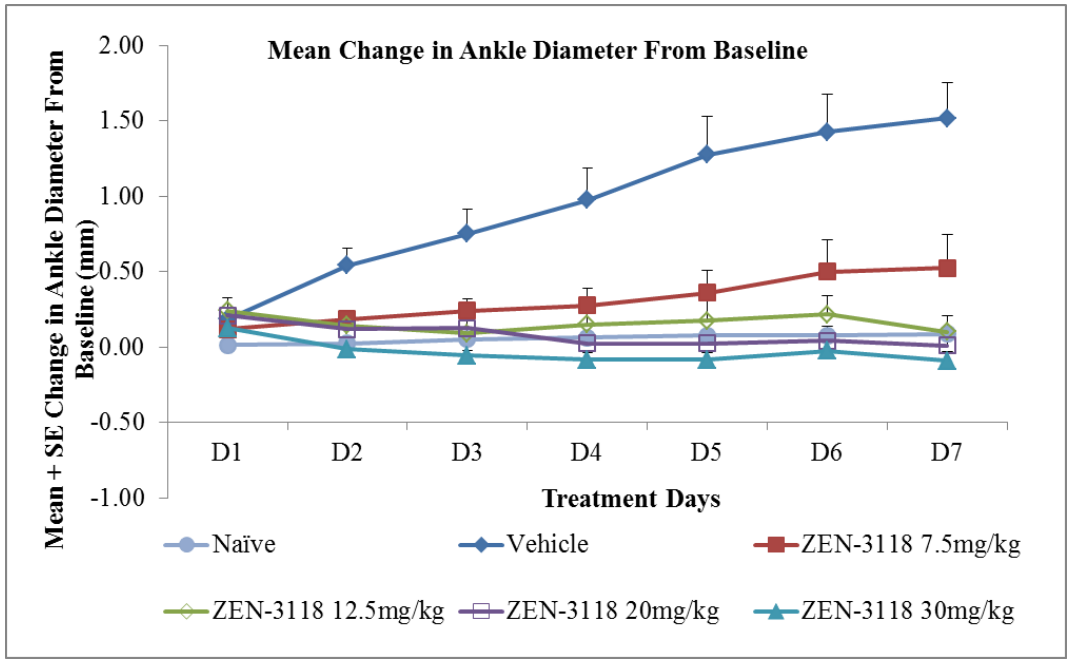


ZEN-3118 is efficacious in rat CIA & mouse EAE at well tolerated doses

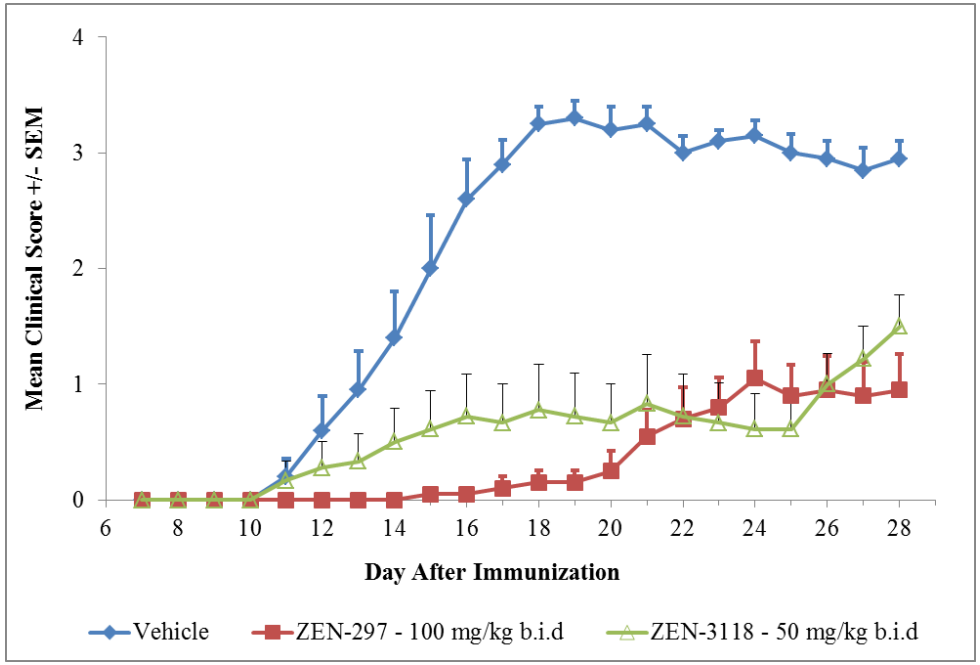
- ZEN-3118 shows dose-dependent inhibition of disease progression in a therapeutic rat collagen-induced arthritis model of rheumatoid arthritis

- Good efficacy in experimental autoimmune encephalomyelitis model of multiple sclerosis

CIA



EAE



ZEN-3365 Summary

BET bromodomains are a novel epigenetic target which regulate super-enhancer acquired oncogenic drivers such as c-MYC and BCL-2

- **Significant MOA rationale and pre-clinical evidence for BET inhibition in leukemia/lymphomas and solid tumors**

Broad and differentiated chemistry platform

Zenith has novel assays and reagents to increase selectivity for BD1 vs BD2 and to elucidate deeper understanding of the biology of BETi

Clinical studies initiating late 3Q 2014 for ZEN-3365 for hematological malignancies

- **Strong PD and efficacy effect in multiple *in vitro* and *in vivo* models**
- **Molecularly defined patient subsets being identified for expansion cohorts**

Solid tumor Phase 1 initiating 1H 2015