TNG260: A novel, orally active, CoREST-selective deacetylase inhibitor for the treatment of STK11-mutant cancers

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Disclosure information

AACR American Association for Cancer Research
ANNUAL MEETING 2023
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Leanne Ahronian

I have the following relevant financial relationships to disclose:

Employee of Tango Therapeutics

Stockholder in Tango Therapeutics

STK11-mutant cancers are resistant to α-PD-(L)1 targeted therapy

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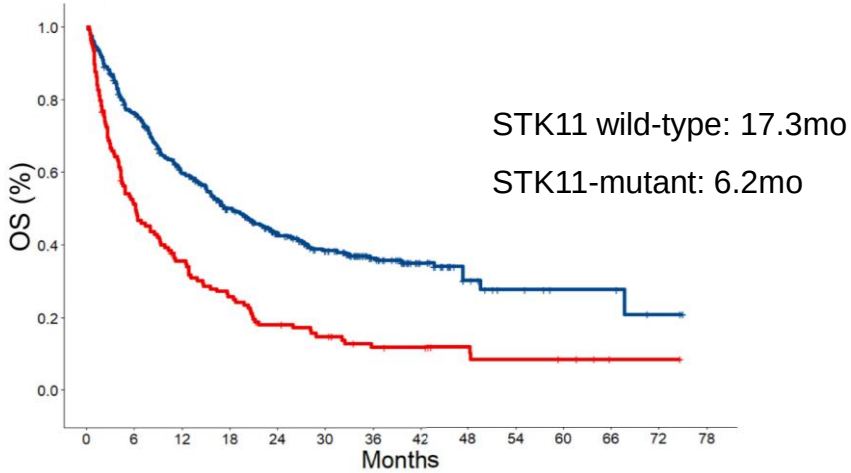
Resistance driven by immune evasion

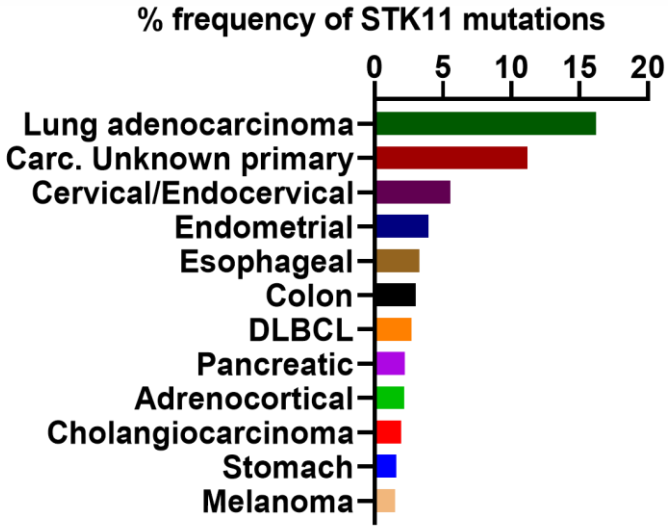
Overall survival after treatment with α-PD-(L)1



KRAS-mutant lung cancer patients, stratified by STK11 status

Ricciuiti et al J. Thorac Onc. 2022

NSCLC is often STK11 mutant (~15%)



TCGA, Ross et al. Oncologist 2020

TNG260 reverses immune evasion caused by STK11 loss-of-function mutations

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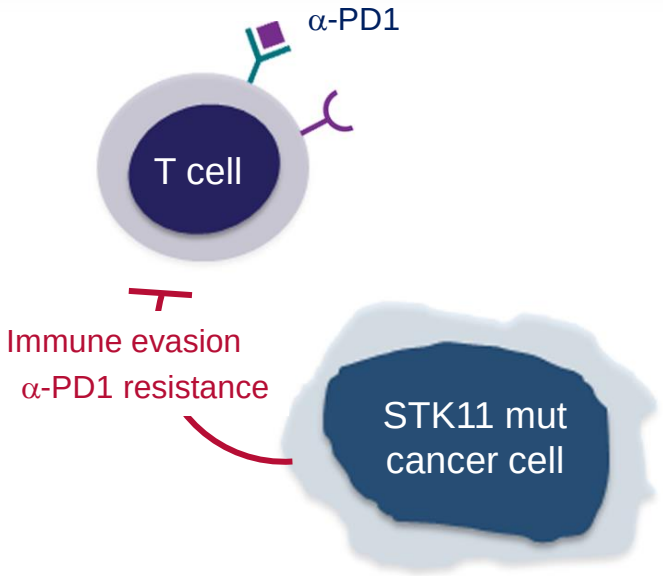
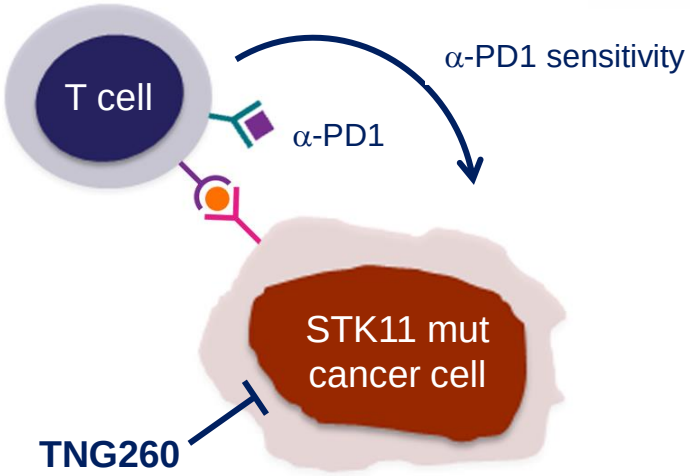
Immune evasion driven by tumor suppressor gene loss



Novel drug targets reverse immune evasion



Selective CoREST inhibition in cancer cells enables immune-mediated cytotoxicity

HDAC1 was identified as an immune sensitizer in an STK11 deficient tumor

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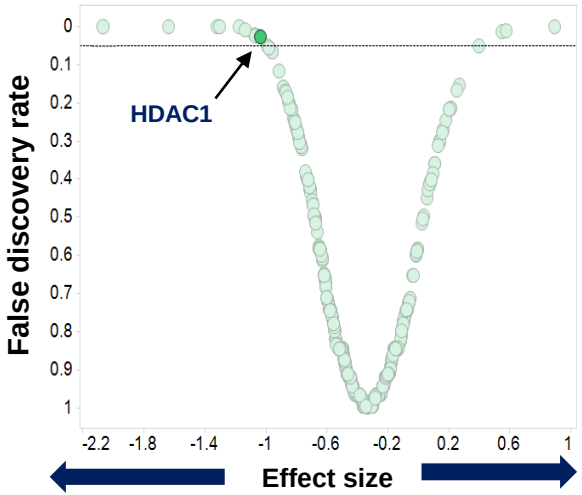
Requires STK11 deletion

STK11-null v. STK11 wild-type

C57Bl/6 mice with α-PD1



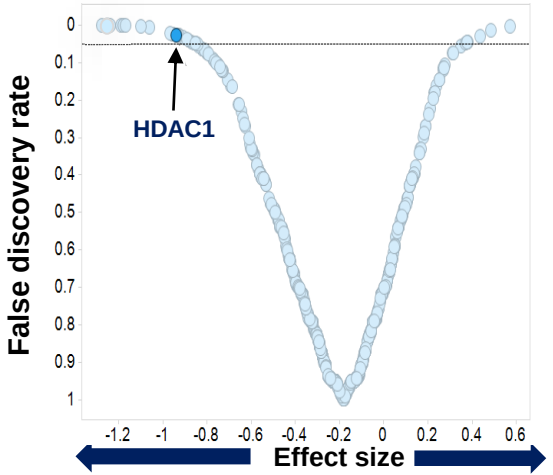
Target knockout enhances killing in STK11- tumors

Target knockout promotes α-PD1 resistance in STK11- tumors

Requires an intact immune system

Immune competent v. nude mouse

STK11-null tumors



Target knockout promotes immune-mediated tumor cell killing

Target knockout impairs immune-mediated tumor cell killing

TNG260 is a CoREST complex inhibitor

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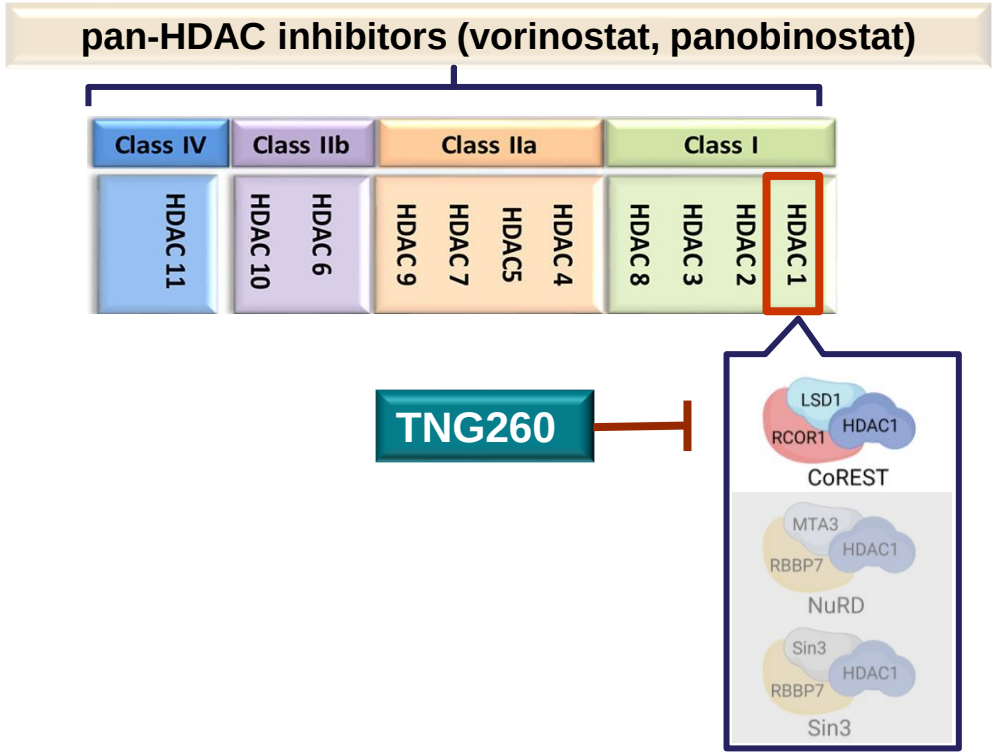

Summary

- Pan HDAC inhibitors are FDA-approved for heme malignancies, where they are directly cytotoxic
- CoREST inhibition provides selective and consistent modulation of immune system genes
- Sin3 is reported to be a major regulator of hematopoietic progenitor cell maturation

TNG260 reverses resistance to α-PD1 driven by STK11 mutation

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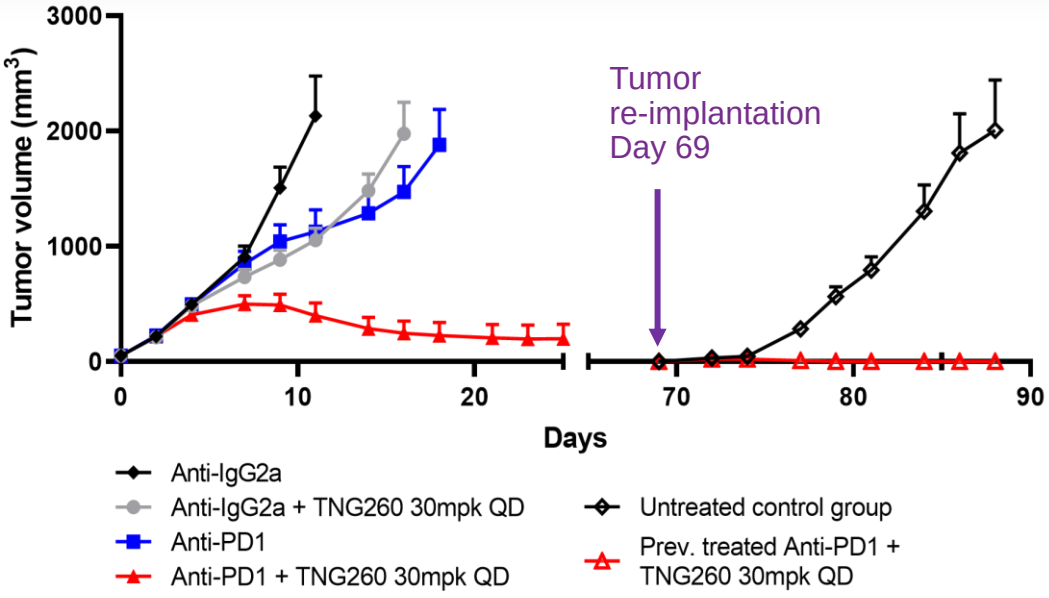
MC38 STK11-mutant syngeneic colon carcinoma model



Summary

- 5/8 mice had complete tumor regression at day 34
- All mice with complete regression remained tumor free off-treatment
- 5/5 mice with complete regression rejected tumor re-implantation

Anti-tumor efficacy of TNG260 is immune-mediated and requires an intact immune system

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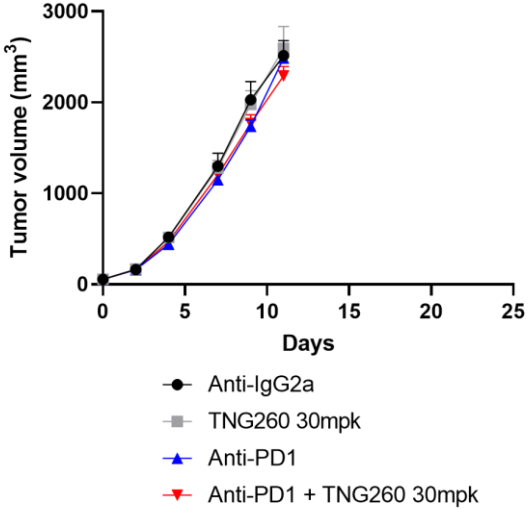
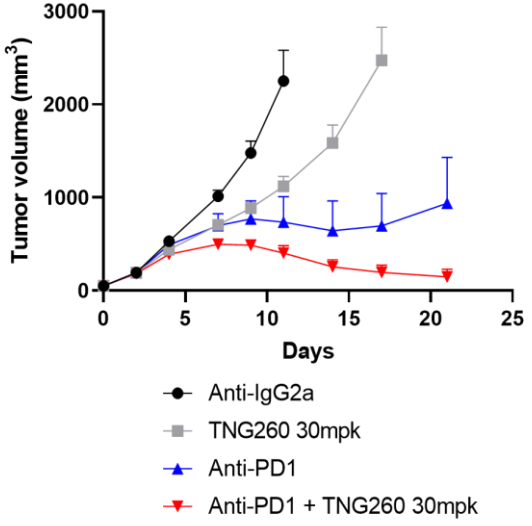
Immunocompromised mice

MC38
(STK11 deficient colon)
BALB/c nude mouse



Immunocompetent mice

MC38
(STK11 deficient colon)
C57BL/6



TNG260 is a potent and selective inhibitor of CoREST deacetylase activity

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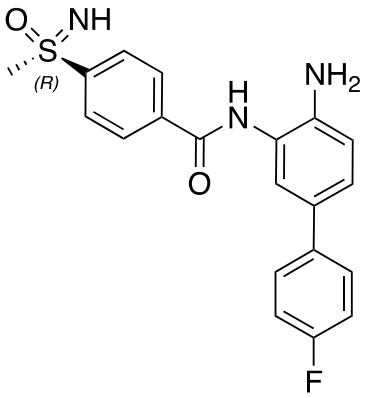
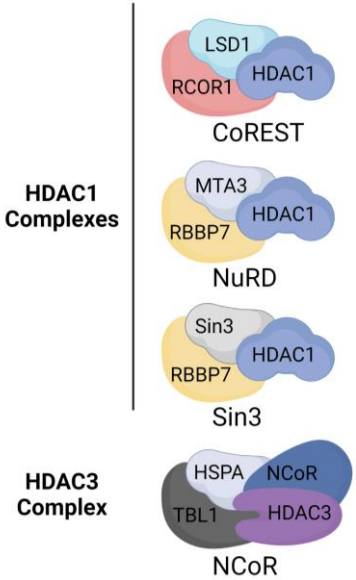
TNG260



Selectivity for the CoREST complex



		CoREST	NCoR	NuRD	Sin3
Pan	Vorinostat	0.06	0.53	0.13	0.16
Class I	Tucidinostat	0.12	0.20	1.40	>100
Class I	Domatinostat	0.09	0.19	30	>100
CoREST	TNG260	0.17	>100	>100	>100

TNG260 inhibits only CoREST

TNG260 is a potent and selective CoREST inhibitor with good drug-like properties

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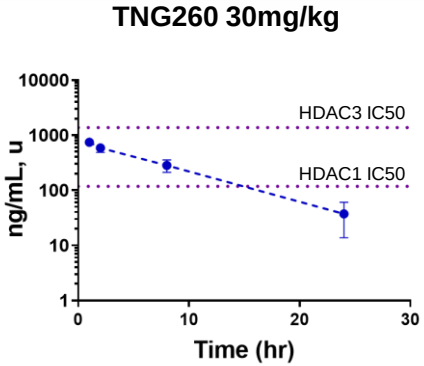
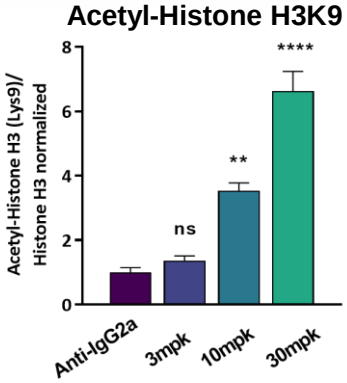
Mouse PK/PD of TNG260





- Day 2 PK samples
- PD evaluated after 7 days QD oral dosing

Pharmacological Properties

Potency	
Cellular IC_{50} of HDAC1	110 nM
Cellular IC_{50} of HDAC3	1070 nM
CoREST IC_{50}	170 nM
IC_{50} of HDAC4-11	>50uM

Properties	
MW, $logD_{7.4}$, TPSA	< 400, 1.9, 96
PO PK (rat, dog, cyno) %F	95, 67, 83
$T_{1/2}$ (hr)	4.8, 8.4, 6.8
CL,p (mL/min/kg)	7.7, 9.6, 9.4
hERG IC_{50}	>30uM
CYP3A4	No signal

Selectivity of TNG260 at efficacious doses supports a positive therapeutic index

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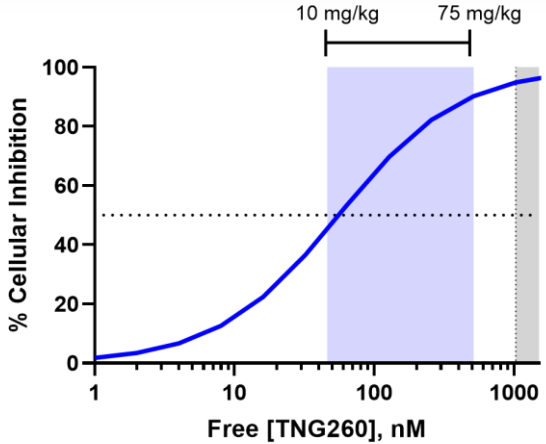
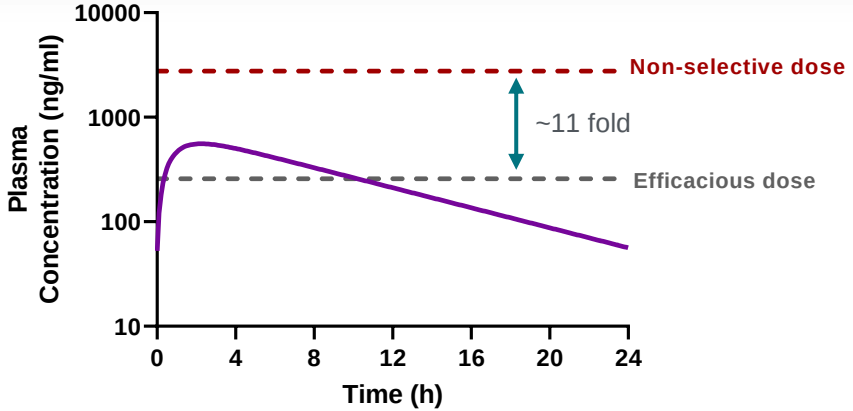
Efficacy of TNG260 in mouse corresponds to HDAC1 IC50



- HDAC1 % Inhibition
- Optimal efficacy range
- Non-tolerated exposures (≥150 mg/kg) correlate with exceeding CoREST-selective doses

Predicted human PK parameters suggest 11-fold therapeutic window



Predicted human PK parameters			
Vdss,p	2.1 L/kg	CL,p	3.8 mL/min/kg
%F	78	MRT	9.5 hrs
$T_{1/2}$	6.6 hrs	Total AUC	6.3 ug*h/mL

TNG260 eliminates Treg infiltration caused by α-PD1 without reducing cytotoxic T cell recruitment

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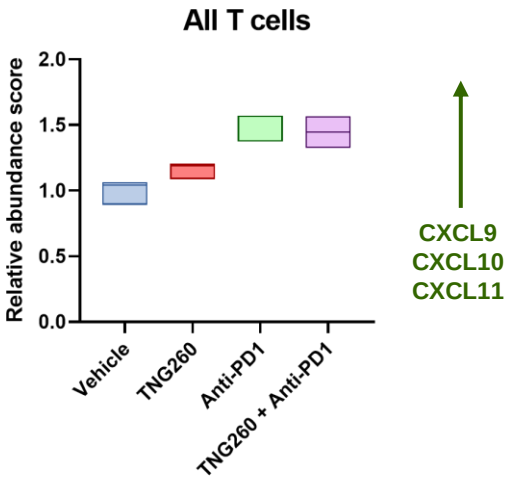
α-PD1 induces tumor cell cytokine secretion that recruits T cells

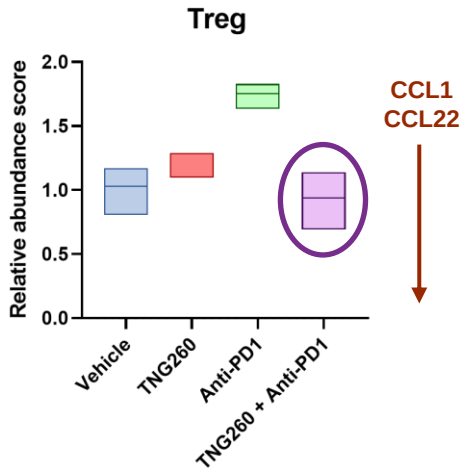
MC38
(STK11 deficient colon)



- CXCL9, CXCL10 and CXCL11 attract cytotoxic T cells
- α-PD1 recruits both cytotoxic T cells and suppressive Tregs

TNG260 eliminates immune suppressive Treg infiltration caused by α-PD1

MC38
(STK11 deficient colon)



- CLL1 and CCL22 attract suppressive Treg cells
- TNG260 prevents α-PD1-driven Treg recruitment

Mechanism of action

- TNG260 causes transcriptional reprogramming in STK11-mut cells
- TNG260-mediated transcriptional changes alter tumor secretion of specific cytokines
- Changes in cytokine secretion caused by TNG260 + α-PD1 change the tumor T cell ratio to strongly favor immune-mediated tumor cell killing

TNG260 selectively regulates immune function

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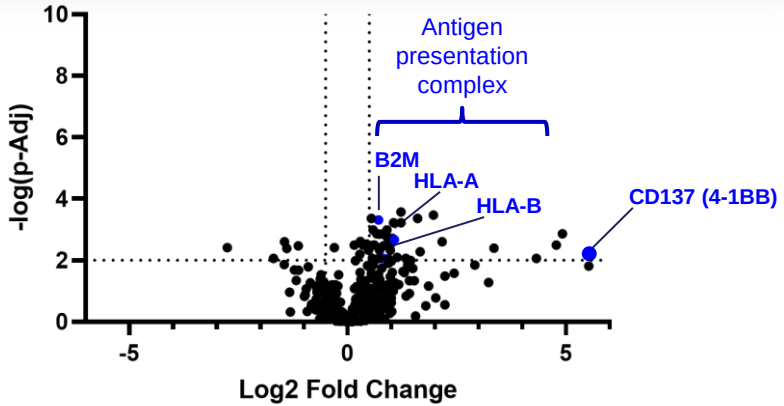
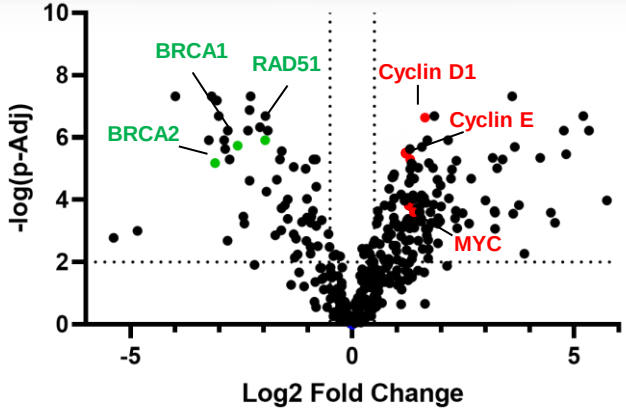
TNG260 (CoREST)
A549 (STK11 mutant cell line)



	Rank
Immune Cell Adhesion and Migration	1
Matrix Remodeling and Metastasis	2
Antigen Presentation	3

Top scoring genes activated by CoREST inhibition are immunomodulatory

Vorinostat (pan-HDAC)
A549 (STK11 mutant cell line)



	Rank
Cell Proliferation	1
DNA Damage Repair	2
Wnt Signaling	3

Top scoring genes activated by pan-HDAC inhibition regulate cell cycling and DNA damage repair

TNG260 is a CoREST inhibitor for STK11-mutant cancer

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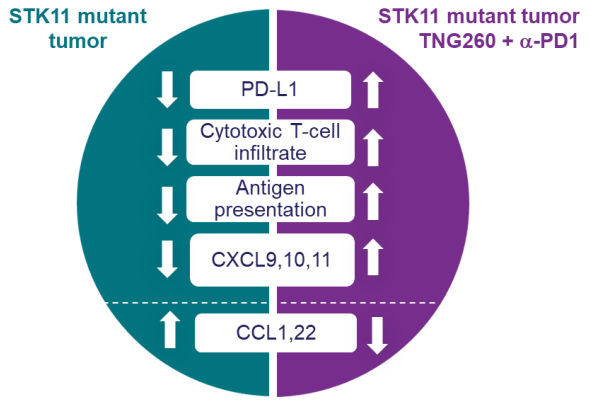
TNG260 reverses key immune evasion mechanisms of STK11-mutant tumors



- HDAC1 was identified as a target that, when inhibited, can reverse immune evasion driven by loss of STK11
- TNG260 is a potent and selective inhibitor of the CoREST complex
- TNG260 is a once daily, oral drug with good pharmacological properties
- TNG260 regulates the expression of genes related to immune function, including antigen presentation
- The combination of TNG260 with α-PD1 drives anti-tumor efficacy in STK11-null mouse models

Tango at AACR

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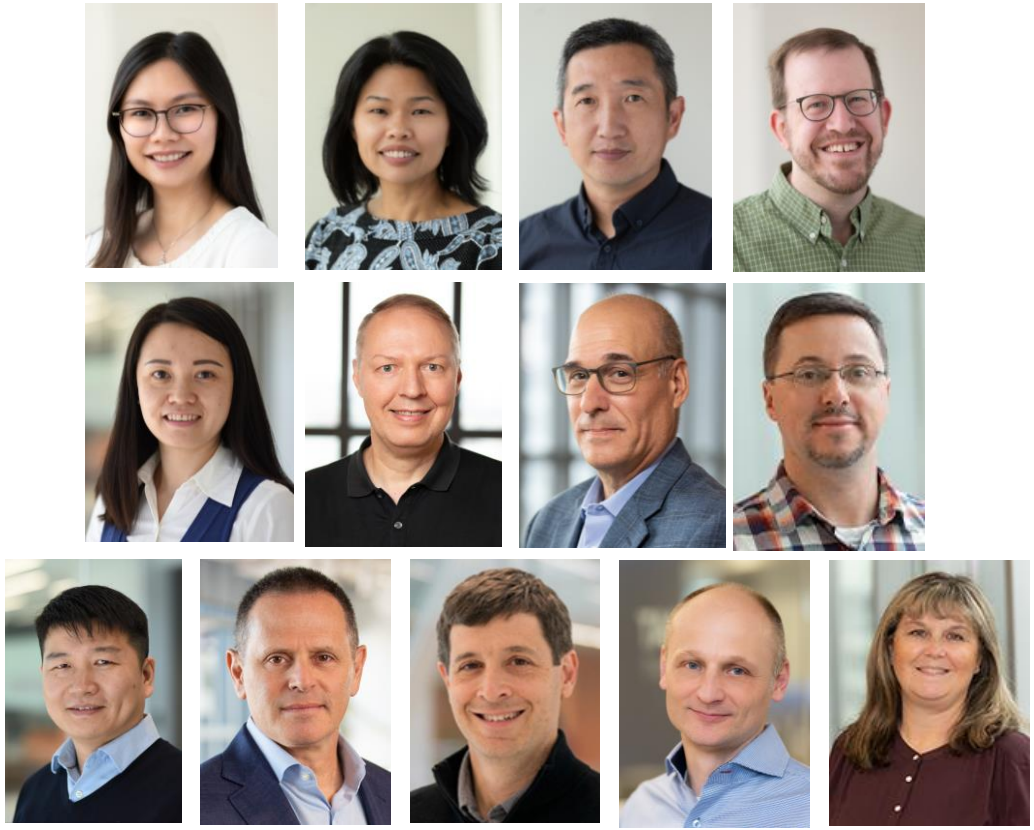
TNG908, a brain-penetrant MTA-cooperative PRMT5 inhibitor, is efficacious in preclinical glioblastoma models
Abstract #: 3452
Session title: Novel Antitumor Agents and Targets
Presenter: Kimberly Briggs, Ph.D., Associate Director, Tango Therapeutics
Session date and time: April 17, 2023, 2:30-4:30 p.m. ET

TNG462 is a potential best-in-class MTA-cooperative PRMT5 inhibitor for the treatment of MTAP-deleted solid tumors
Abstract #: 4970
Poster session date and time: April 18, 2023, 1:30-5:00 p.m. ET

Characterization of the clinical development candidate TNG348 as a potent and selective inhibitor of USP1 for the treatment of BRCA1/2mut cancers
Abstract #: 4968
Poster session date and time: April 18, 2023, 1:30-5:00 p.m. ET

Acknowledgements



For additional questions:
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