

AACR-NCI-EORTC Virtual International Conference on

# MOLECULAR TARGETS AND CANCER THERAPEUTICS

October 7-10, 2021



## CRISPR screens identify sensitizers to trametinib in KRAS mutant cancer cell lines

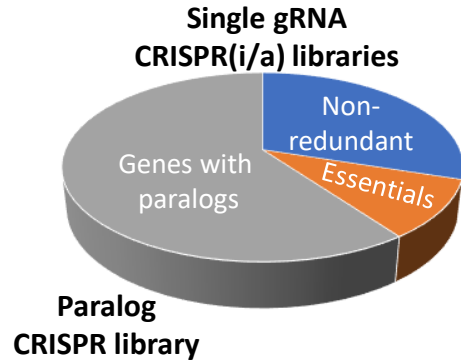
Silvia Fenoglio, Aileen Cristo, James Tepper, Teng Teng, Samuel Meier, Ashley Choi, Hongxiang Zhang, Shan-chuan Zhao, Shangtao Liu, Yi Yu, Leanne Ahronian, Dan Aird, Nikita M. Das, Robert Tjin Tham Sjin, Jannik N. Andersen, Alan Huang, Fang Li, Xuewen Pan

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# The Tango Therapeutics CRISPR platform

## Expansive target space



## Enabling technologies

Optimized systems (Cas9/enCas12a)  
Combo-CRISPR  
CRISPR-UMI  
CRISPR-StAR

Isogenic  
screens  
→  
with or  
without a  
compound

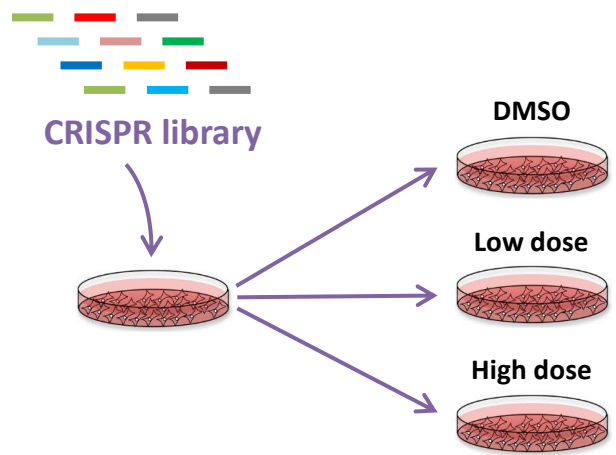
## Diverse screening formats

- 2D synthetic lethality screens
- 3D synthetic lethality screens
- FACS-based screens
- In vitro primary T-cell screens
- T-cell/tumor cell coculture screens
- *In vivo* synthetic lethality screens
- *In vivo* immune evasion screens

Single gene or  
Mini-pool  
target  
validation  
*in vitro* & *in vivo* with or  
without cDNA  
rescue



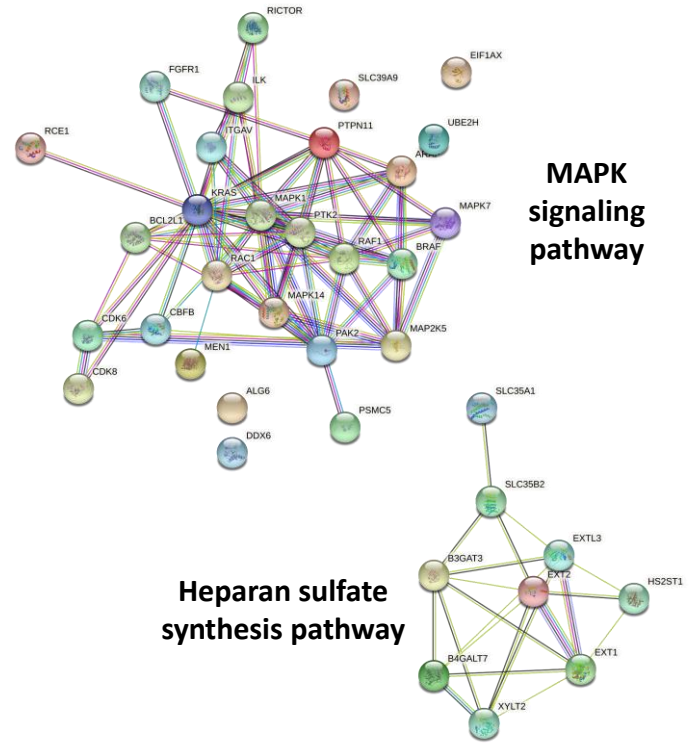
# Trametinib CRISPR screens in NSCLC and PDAC cell lines



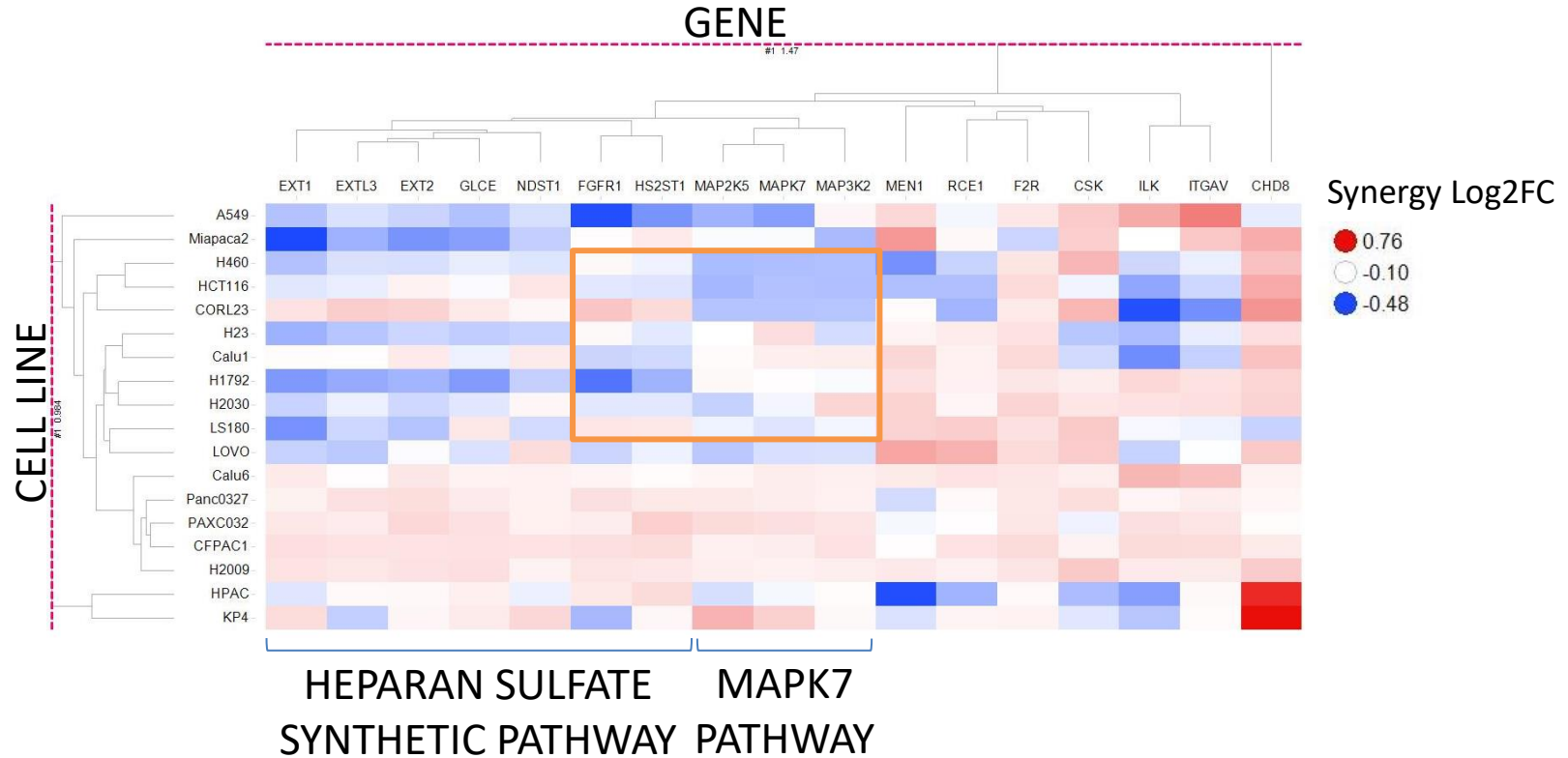
Cell line	Histology	KRAS status
A549	NSCLC	G12S/G12S
NCI H1355	NSCLC	G13C/WT
NCI H358	NSCLC	G12C/WT
MIA PaCa-2	PDAC	G12C/G12C
KP4	PDAC	G12D/WT

gene	A549	H1355	H358	KP4	MIA PaCa-2
MAPK1	1	16	3	1	1
FGFR1	2	2	2619	167	109
RAF1	3	1	7	3	11
BRAF	4	5	6	2	38
MAPK7	5	1695	1	453	3081
HS2ST1	6	11	341	73	28
SLC35B2	7	9	63	15	10
RCE1	8	23	740	13	84
EXTL3	9	35	276	40	17
PTPN11	11	6	8	38	5
MAP2K5	14	257	5	3038	246
ARAF	15	100	149	9	96
EXT1	16	39	987	563	3
RICTOR	17	347	4094	24	4530
PAK2	21	4482	887	139	12
EXT2	22	13	98	78	8
BCL2L1	23	15	108	498	97
SLC35A1	25	30	81	3069	1292
CDK8	26	140	4536	1712	4007
KRAS	28	46	43	21	94
PSMC5	29	69	4422	10	4287
SLC39A9	30	45	4581	4265	22
ALG6	31	218	4	464	60
CDK6	39	173	82	4	44
MAPK14	42	14	58	998	24
XYL12	47	26	129	19	7
B4GALT7	71	24	156	171	14
UBE2H	105	3	14	153	4210
DDX6	139	27	30	92	4297
B3GAT3	940	18	83	33	2
MEN1	2189	19	10	4548	35
PTK2	2439	4368	69	6	18
CBFB	4264	1377	17	1056	20
RAC1	4383	3566	9	11	4
ILK	4482	33	20	252	210
ITGAV	4485	1034	23	18	25
EIF1AX	4495	12	4596	93	26

Depleting genes **FDR<0.01** **0.01<FDR<0.05**  
 Enriching genes **FDR<0.05**

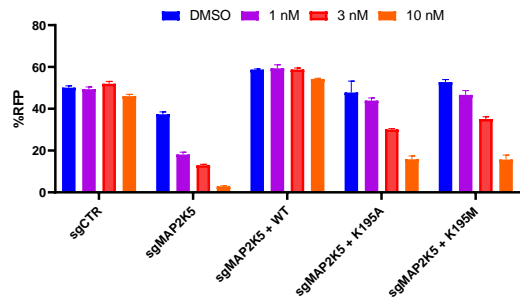
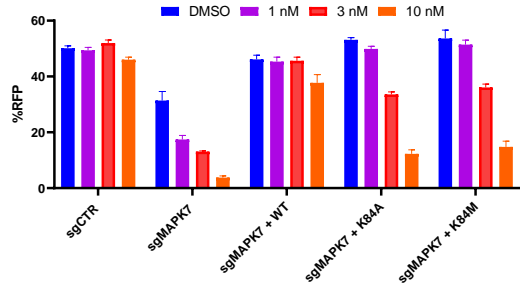


# Target validation using minipool screens in an expanded cell line panel

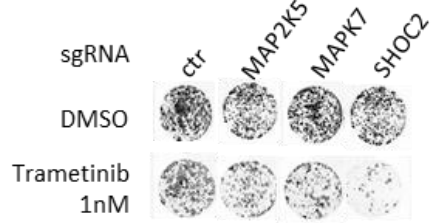


# SHOC2, MAPK7, MAP2K5 are validated sensitizers to MEKi

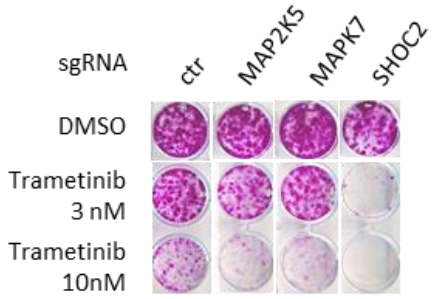
## COMPETITION ASSAY A549



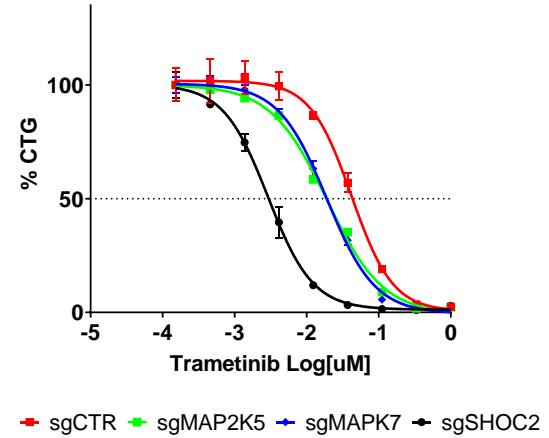
## NCI H358



## A549



## NCI H358



# Conclusions

- CRISPR screening identifies gene KO that enhance the response to trametinib
- Distinct signaling pathways are uniquely involved in trametinib resistance in different cell lines
- MAPK7, SHOC2 and HS2ST1 are validated sensitizers to trametinib (Leanne Ahronian, poster P146 for HS2ST1 validation)



# Thank you!

- Tango Therapeutics:



- Contract research partners: Scientific teams at ChemPartner

## Contact information

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