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# VRK1 is a Novel Synthetic Lethal Target in VRK2-methylated Glioblastoma

Julie Shields, Samuel R. Meier, Justin Engel, Madhavi Bandi, Maria L. Dam Ferdinez, Wenhai Zhang, Shan-chuan Zhao, Minjie Zhang, Ashley Choi, Yi Yu, Xuewen Pan, Brian McMillan, Brett Williams, Robert Tjin Tham Sjin, Douglas Whittington, Erik Wilker, Alan Huang, Fang Li and Natasha Emmanuel

TANGO THERAPEUTICS
100 Binney Street, Suite 700
Cambridge, MA 02142
+1-857-320-4900
info@tangotx.com

# VRK1 emerges as a novel synthetic lethal target in TANDEM, Tango's proprietary cancer dependency map

**CRISPR screens +/- anchor drug**
Cancer cell lines
Isogenic cell lines
Immune cells
*In vivo* syngeneic cancer models

Tango Data

Public Data

Tango Cancer Dependency Map Database

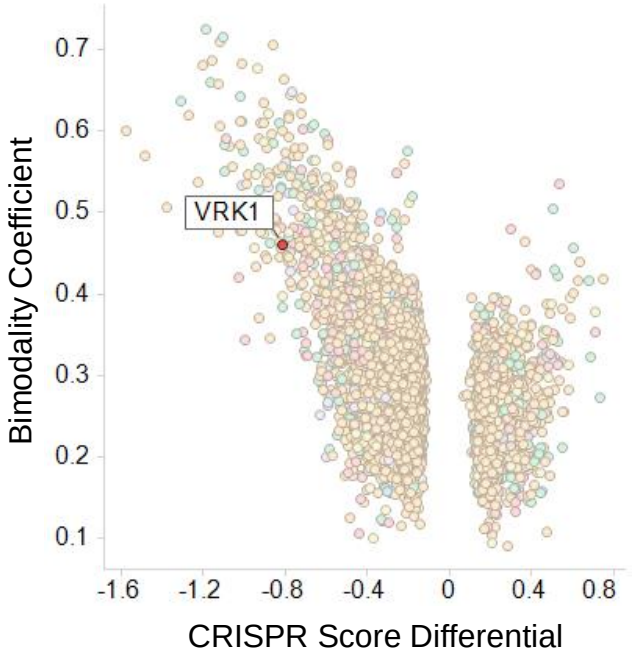
TANDEM

**Functional**
Achilles CRISPR
Sanger CRISPR
D2 RNAi
Drug Sensitivity

**Genomic**
Mutation
Copy Number
Methylation
Fusion

**Tractability**
CanSAR
Open Targets

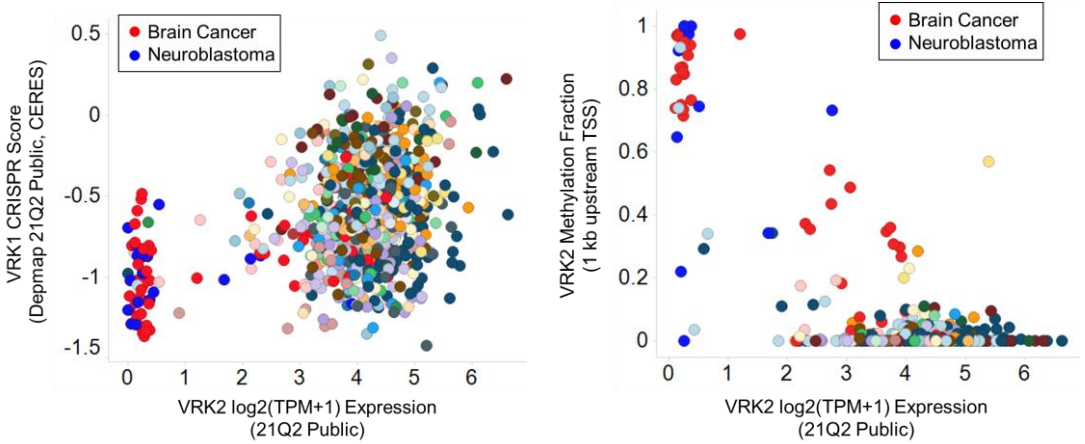
TANDEM Targets



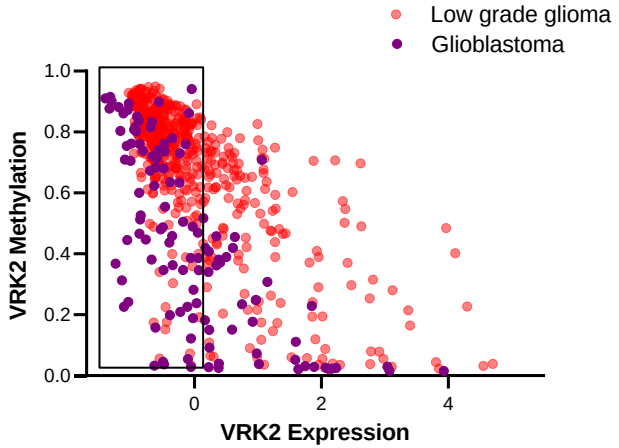

Note: Genes are color-coded by tractability

# VRK2-methylated glioblastoma and neuroblastoma cell lines are sensitive to VRK1 loss

CCLE cell line data



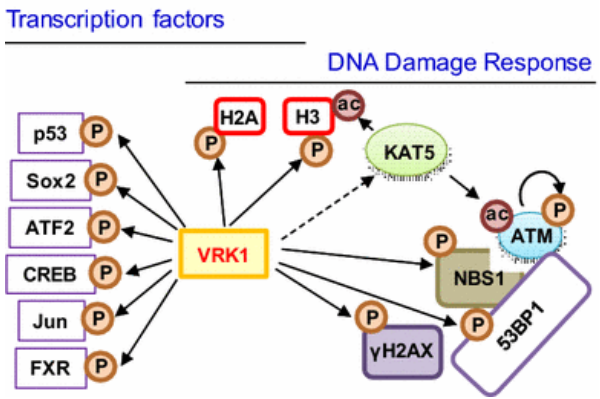

TCGA tumor data




- ~ 60% of brain tumors have low VRK2 expression due to aberrant promoter methylation
- VRK1 is a potential synthetic lethal target in VRK2-methylated brain cancer

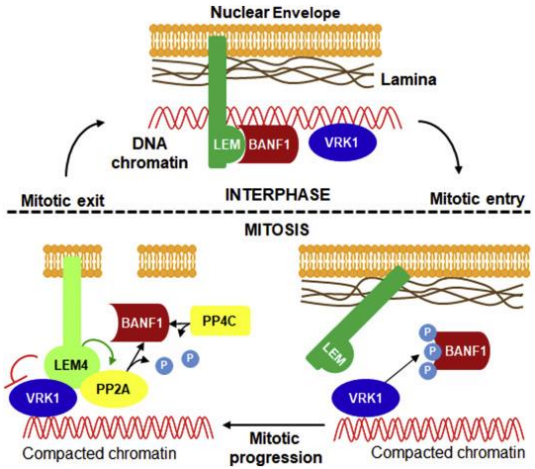
# VRK1 is a mitotic kinase with roles in transcription factor regulation and DNA damage response

VRK1 substrates



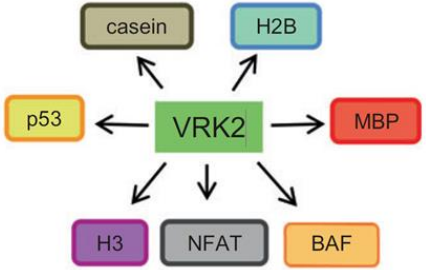

Campillo-Marcos et al, 2018

Nuclear Envelope Formation




Campillo-Marcos et al, 2021

VRK2 substrates

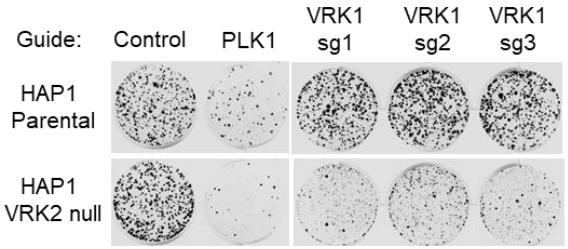


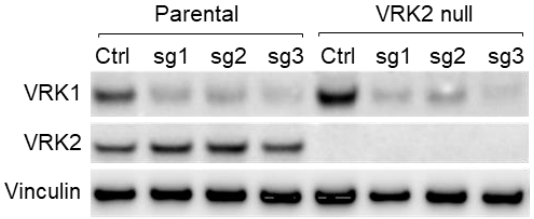

Monslave et al, 2018

VRK1 and VRK2 are paralogs with some overlapping roles

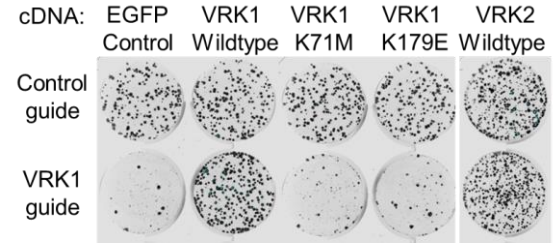
# VRK1 is synthetic lethal with VRK2, and the lethality is dependent on VRK1 kinase activity

VRK1 knockdown in HAP1 isogenic cell line pair

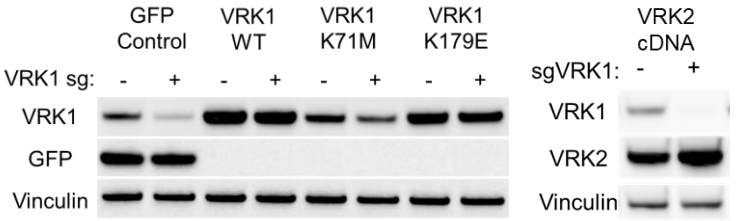



Rescue experiments in HAP1 VRK2null cell line

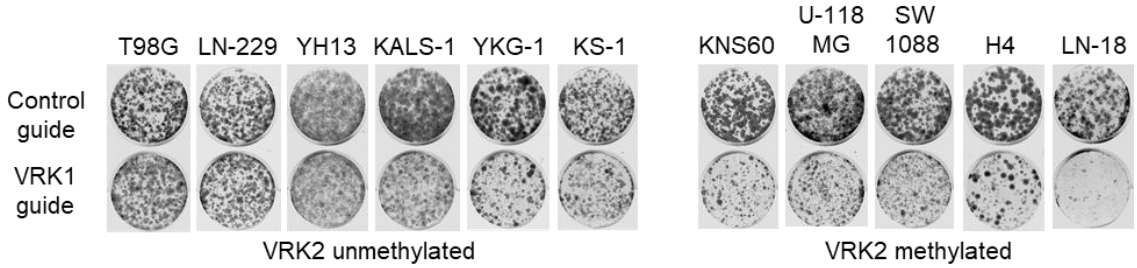


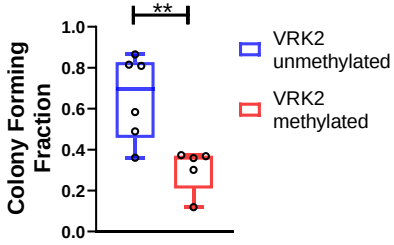

K71M - kinase dead mutant
K178E - kinase inactive mutant



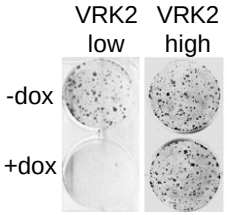
# VRK2-methylated glioblastoma cell lines are sensitive to VRK1 knockdown *in vitro* and *in vivo*

VRK1 knockdown in GBM cell line panel *(in vitro)*

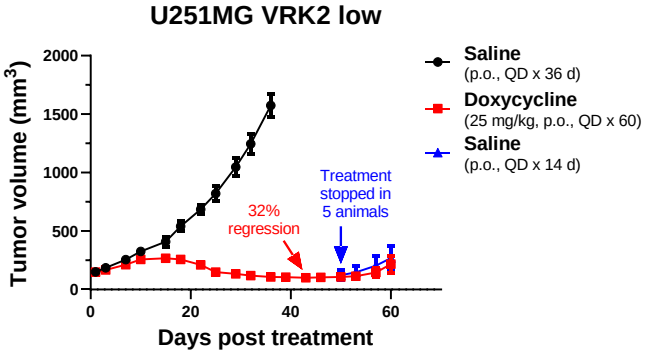


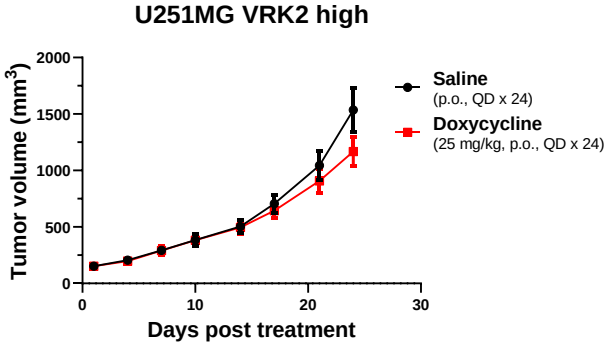




VRK1 knockdown in GBM isogenic cell lines *(in vivo)*




U251MG
Dox-inducible
VRK1 knockdown*

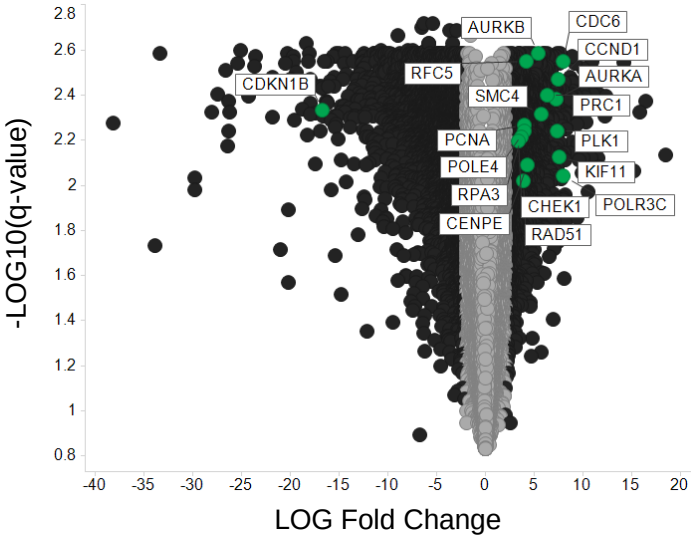


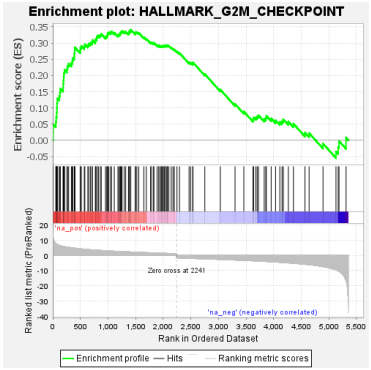



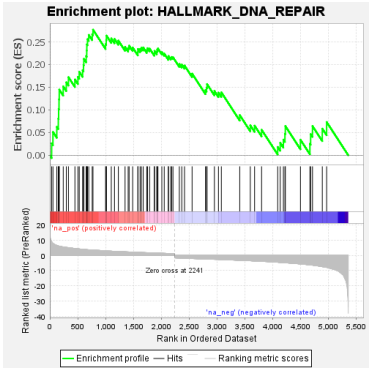

*VRK1 knockdown and VRK2 rescue validated by immunoblotting (*in vitro* and *in vivo*)

# Accumulation of proteins and phospho-proteins involved in G2/M arrest and DNA repair pathways

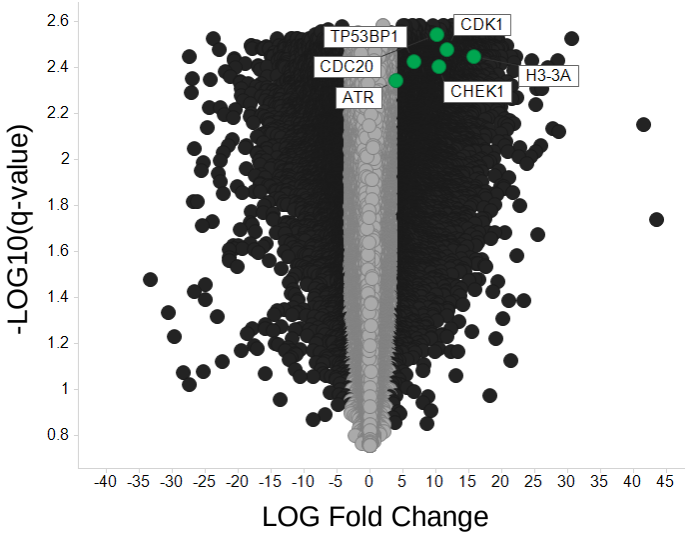
Total Proteomics
VRK2 low vs VRK2 high




Phospho Proteomics
VRK2 low vs VRK2 high



# Summary

- VRK1 is synthetic lethal in VRK2-methylated glioblastoma and VRK1 kinase activity is necessary for the synthetic lethal interaction
- VRK1 knockdown in a VRK2-methylated glioblastoma cell line results in G2/M arrest and subsequent DNA damage
- These results suggest that inhibiting VRK1 kinase activity could be a viable treatment for VRK2-methylated glioblastoma

# Acknowledgements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- Broad Institute: Maria “Masha” Alimova


**Contact information**


- Tango Therapeutics: info@tangotx.com