18th International Myeloma Workshop

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Targeting GCK in RAS-mutant multiple myeloma offer a promising therapeutic approach

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Conflict-of-interest disclosure

S. Lentzsch reports Caelum Biosciences equity ownership and membership on Caelum Bioscience's board of directors or advisory committees; consultancy for Janssen, Takeda, GSK, Antengene, Adaptive and Sorrento and received research funding from Karyopharm and Sanofi.

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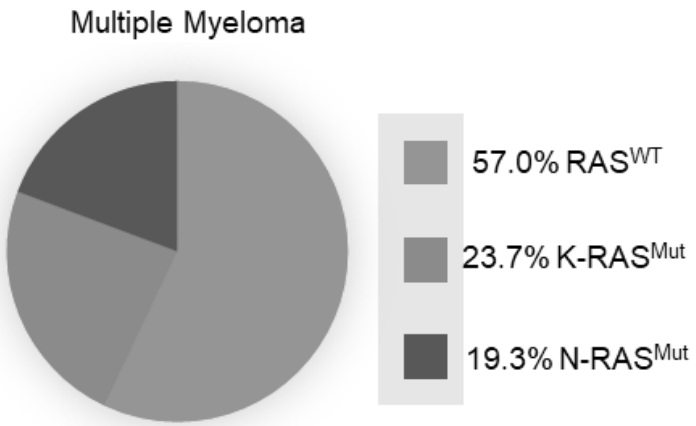
C.M: Sanofi full time employee.

The remaining authors declare no competing financial interests.

RAS mutation in Multiple Myeloma

A.



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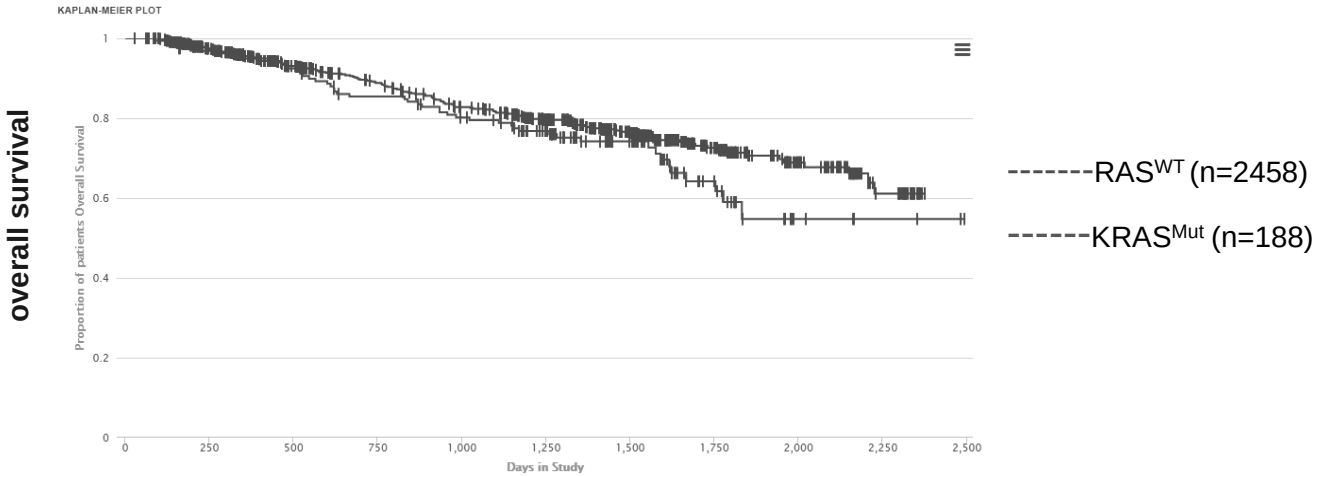

CoMMpass IA15

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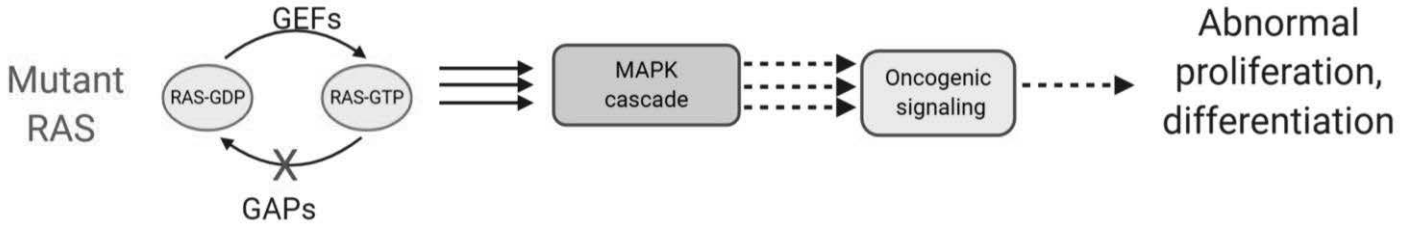
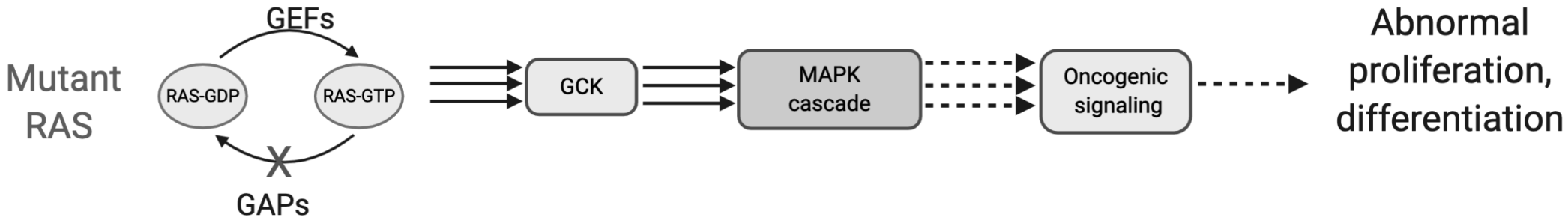


GCK is a novel therapeutic target in MM with RAS mutation

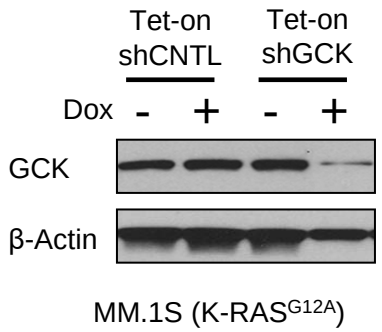


- Germinal Center Kinase (GCK), also named MAP4K2, is an upstream activator in the MAPK pathway
- GCK is predominantly and highly expressed in the germinal center of B cells
- GCK participates in B cell differentiation into plasma cells
- GCK is a potential therapeutic target in colon cancer, DLBCL, AML and ALL

GCK is critical for proliferation and survival of RAS^{Mut} MM cells

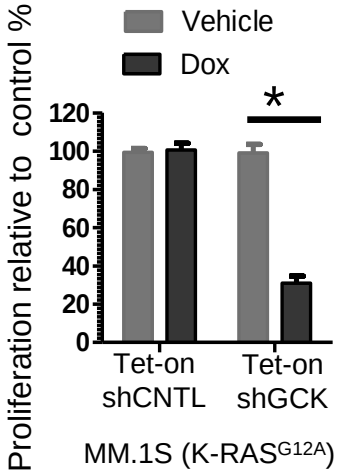
RAS ^{Mut}

A.



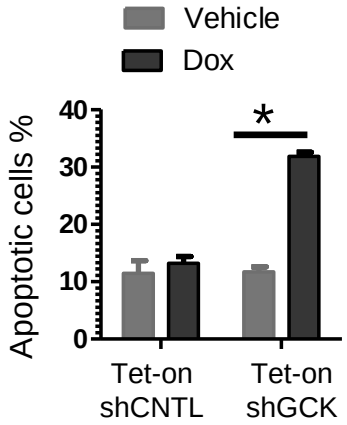
MM.1S (K-RAS^{G12A})

B.



MM.1S (K-RAS^{G12A})

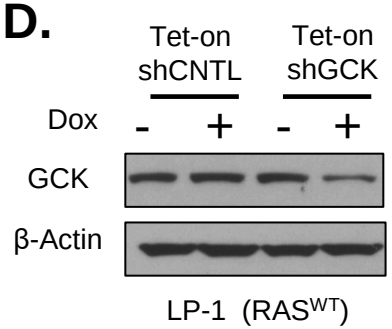
C.



MM.1S (K-RAS^{G12A})

RAS ^{WT}

D.



LP-1 (RAS^{WT})

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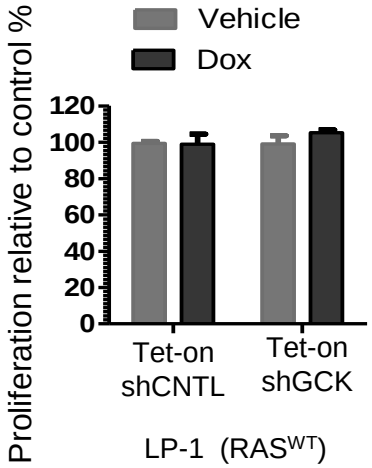
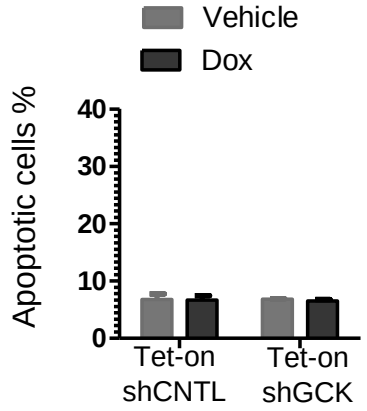


LP-1 (RAS^{WT})

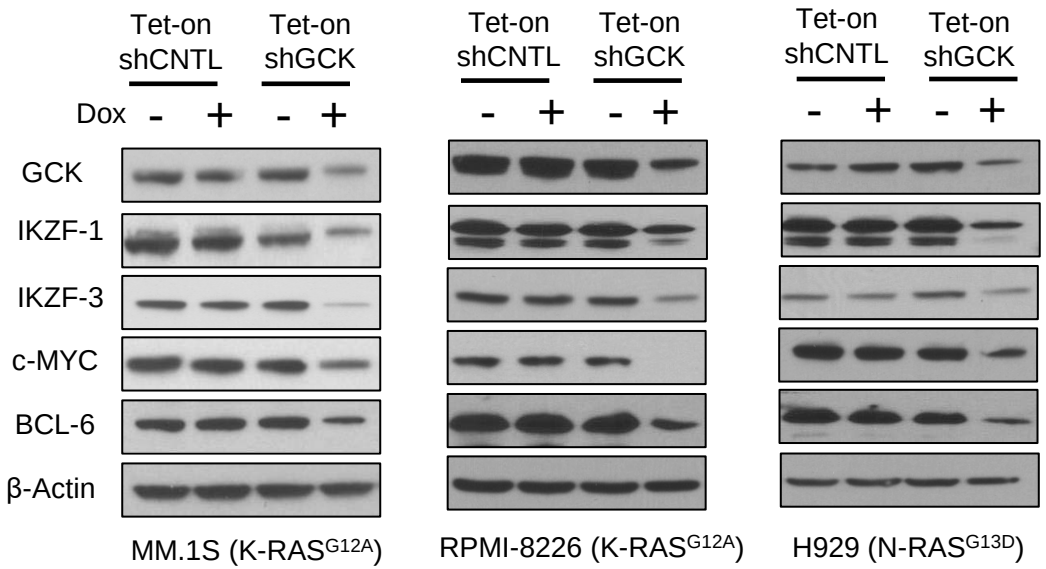
F.



LP-1 (RAS^{WT})

Knockdown of GCK decreases c-MYC, IKZF1, IKZF3 and BCL6 expression in RAS^{Mut} MM cells

A.



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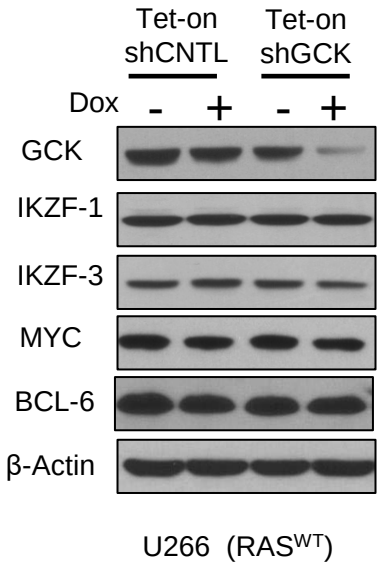

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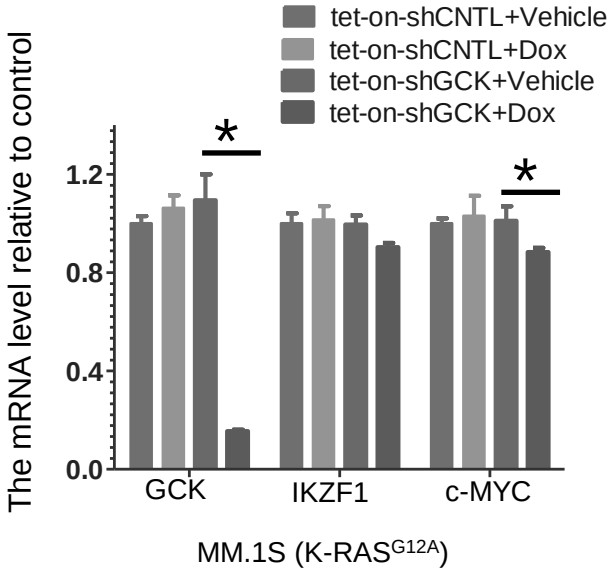
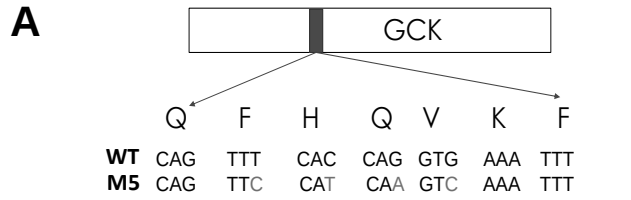
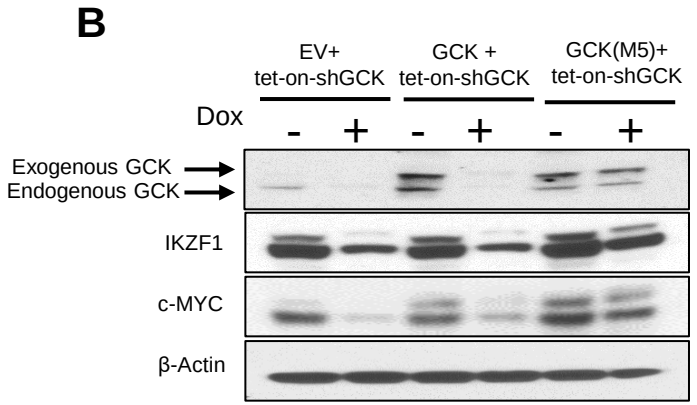
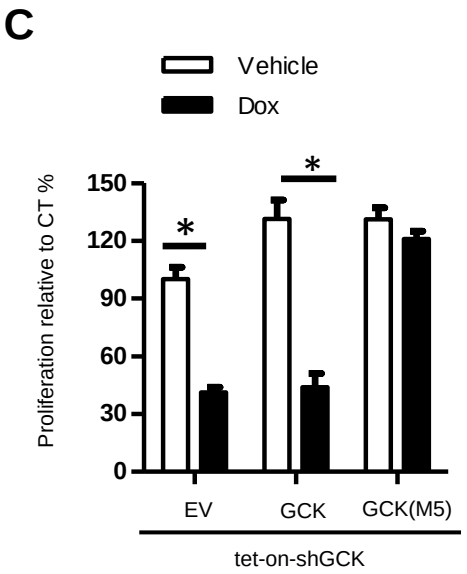
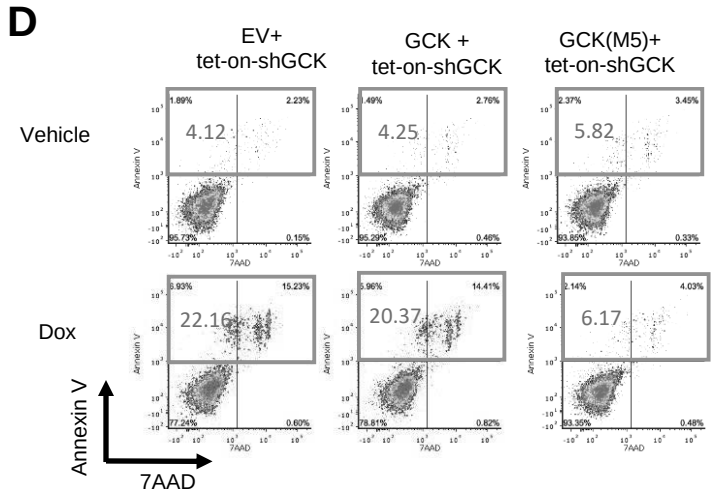


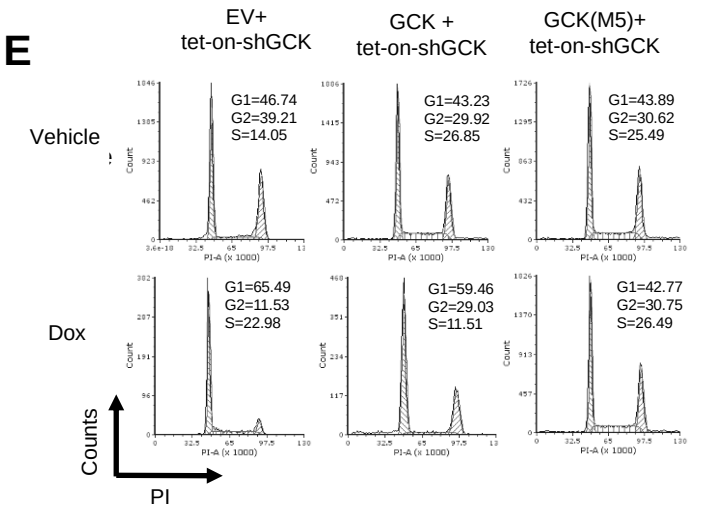
Rescue experiments exclude possible off-target effects of GCK shRNA





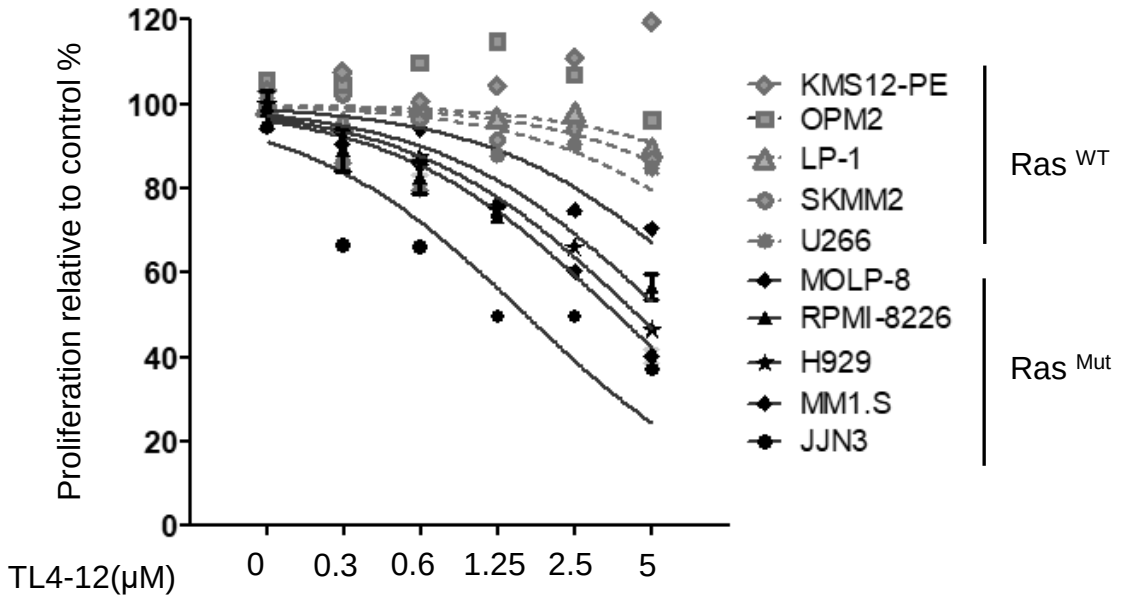






Pharmacological blockage of GCK activity inhibits the growth of RAS^{Mut} multiple myeloma

A.



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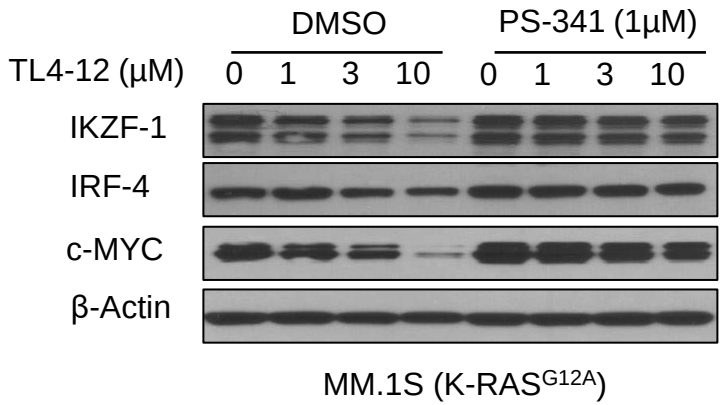
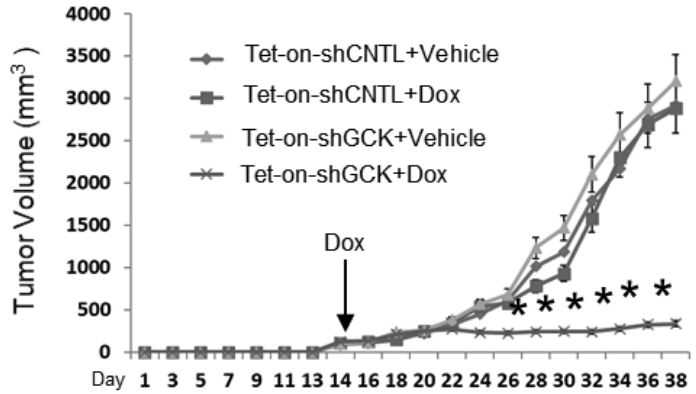


MM.1S (K-RAS^{G12A})

GCK is critical for MM tumor growth in vivo

A.



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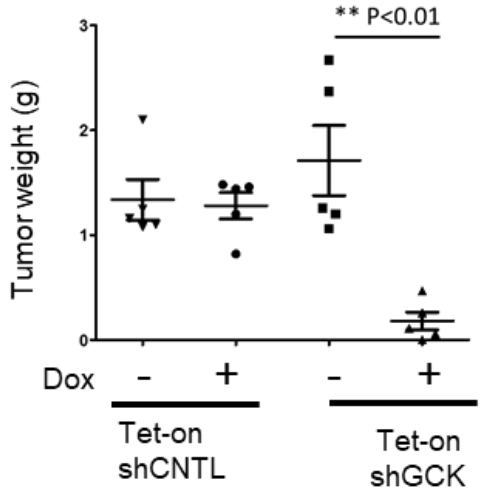

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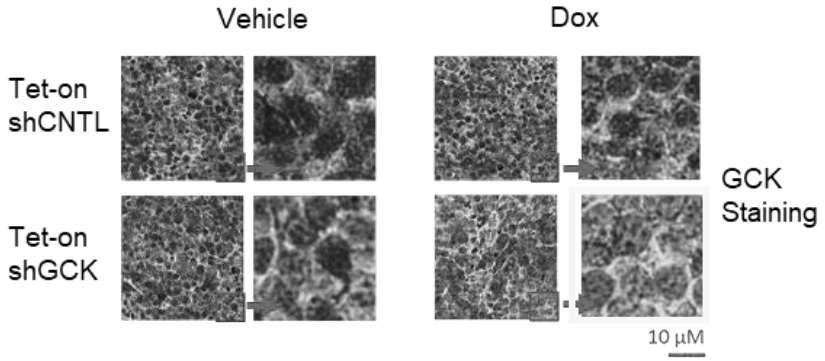

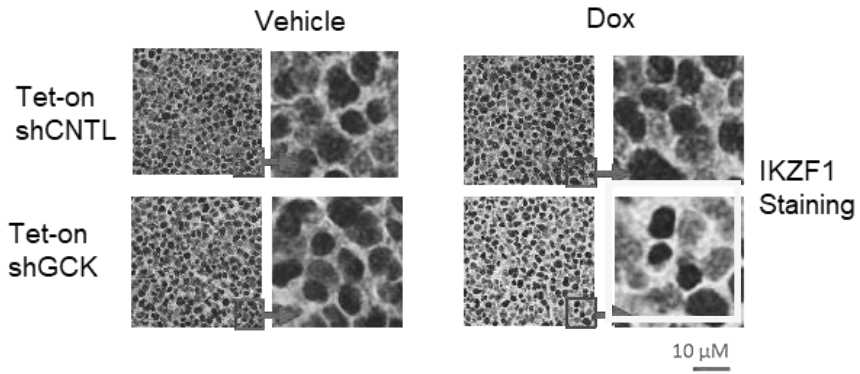

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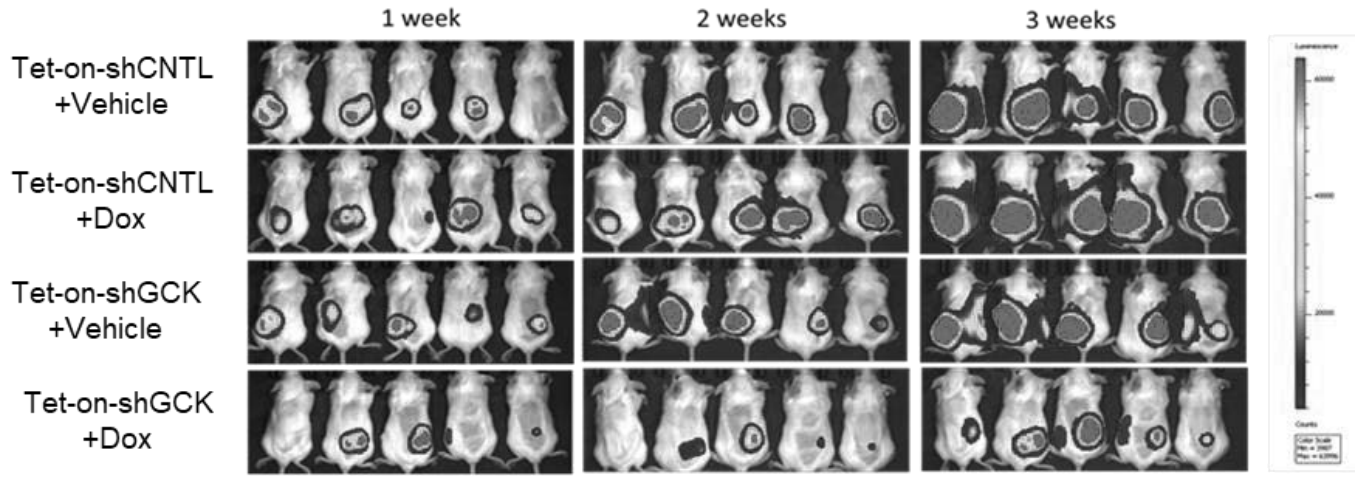
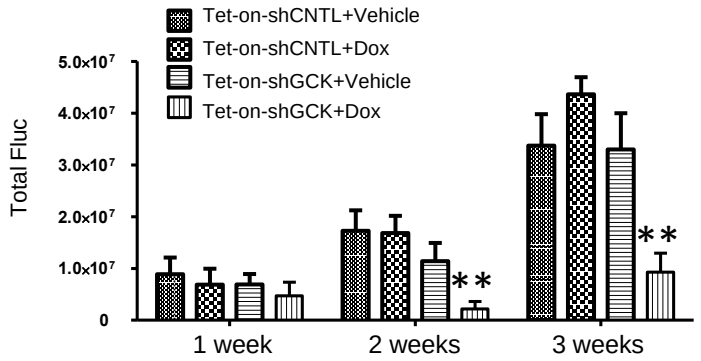
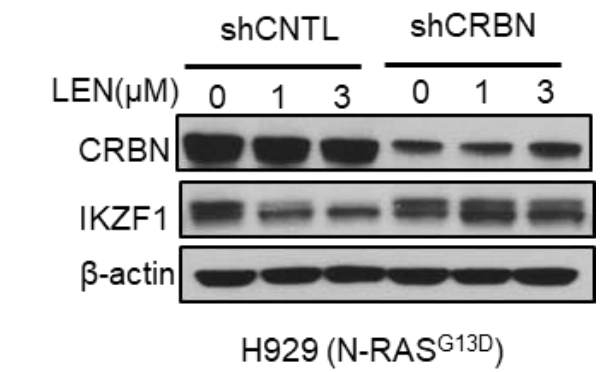
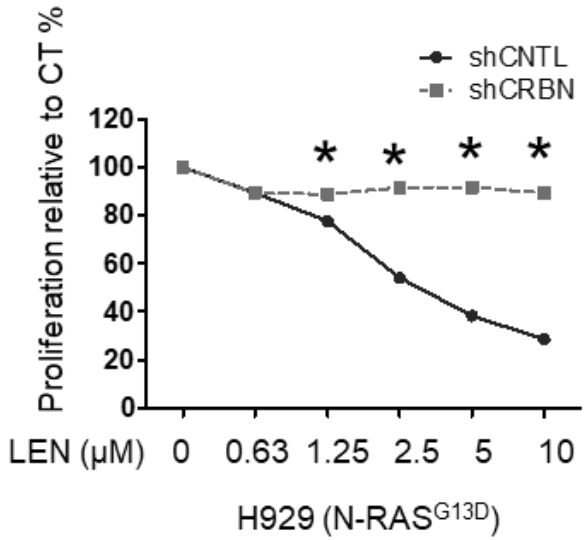




GCK Inhibition overcomes resistance to lenalidomide in MM

A.





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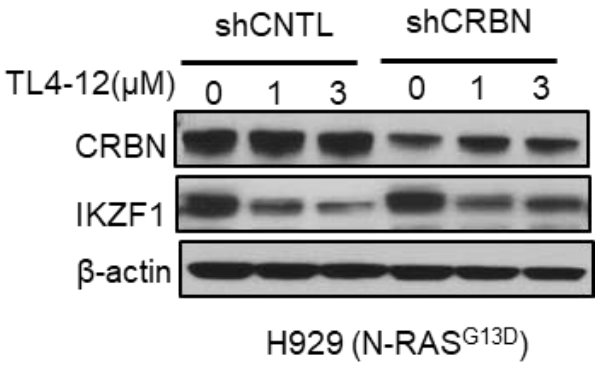
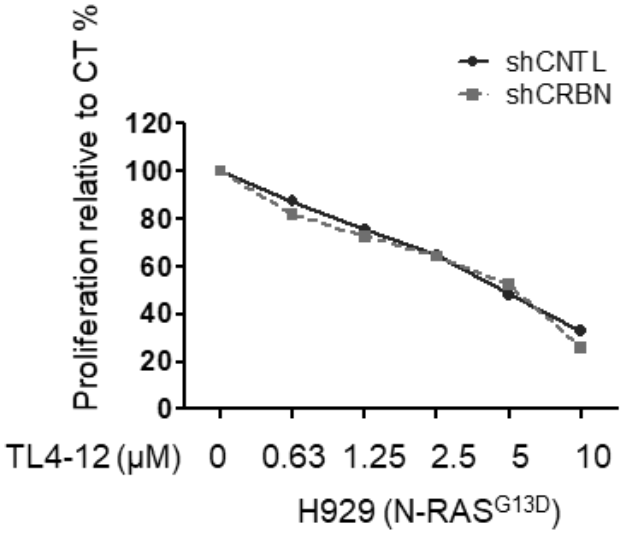
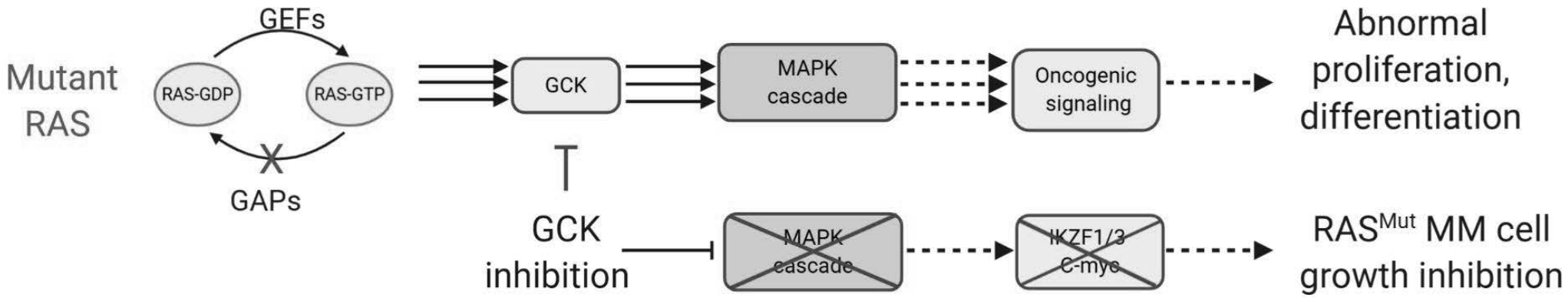




Conclusion


Mutant RAS
GEFs
RAS-GDP
RAS-GTP
GAPs
GCK
MAPK cascade
Oncogenic signaling
Abnormal proliferation, differentiation
GCK inhibition
MAPK cascade
IKZF1/3 C-myc
RASMut MM cell growth inhibition

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SANOFI

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