



Investigating the Therapeutic Potential of Molecularly Targeted Therapy in Pediatric Spindle Cell Rhabdomyosarcoma



Research Week
06/12/20

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Objectives

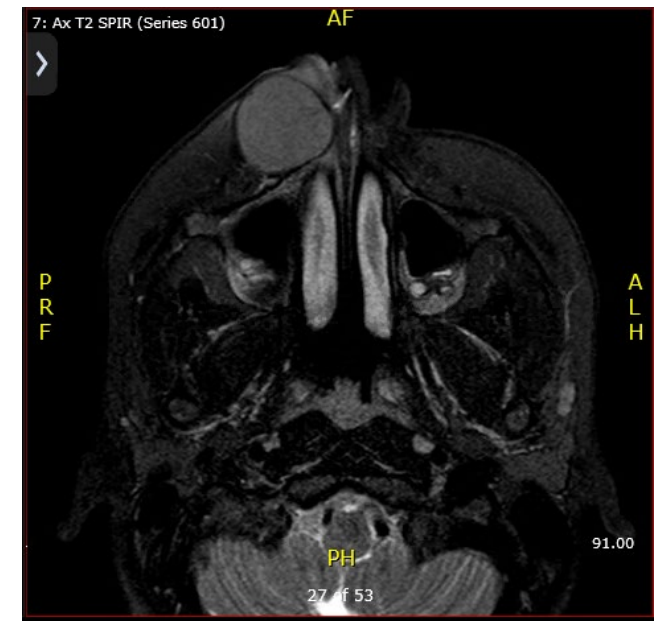
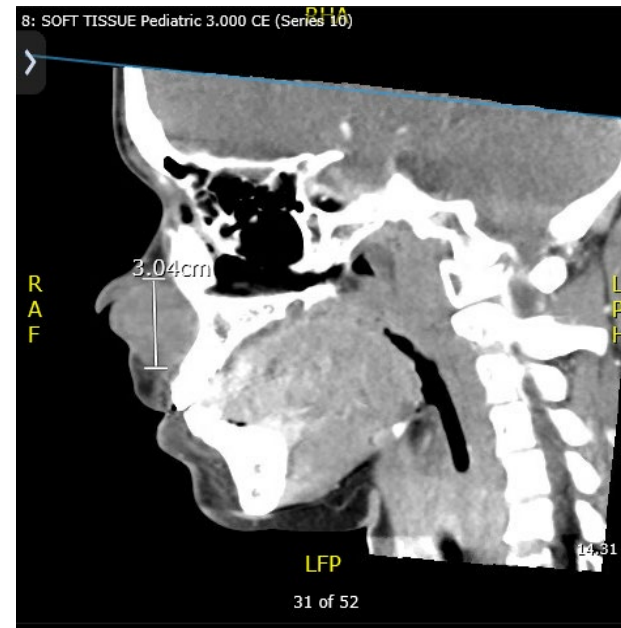


- Discuss a patient case of spindle cell rhabdomyosarcoma and patient derived cell line SARC001
- Review known clinical characteristics and molecular aberrations in spindle cell rhabdomyosarcoma
- Describe *in vitro* drug effects on PIK3CA/AKT pathway in SARC001
- Determine drug dose responses in SARC001

+ Patient Presentation



- 15 yo male with no significant PMH presenting with large pedunculated mass in the right nare.
- 2 weeks later mass continued to grow
- Evaluated in the DCH ED
- Underwent biopsy





Diagnosis



■ Pathology Report:

- Rhabdomyoblasts scattered throughout biopsy and strap cells consistent with rhabdomyoblastic differentiation
 - Patchy expression for desmin
 - Punctate scattered nuclear expression for myogenin
 - Strong diffuse nuclear staining for MYOD1
- ## ■ Diagnosis: Embryonal rhabdomyosarcoma, spindle cell variant

+ Tumor Progression

3/04/19



3/07/19 (week 1)



3/21/19 (week 3)



4/01/19 (week 4)



4/16/19 (week 6)



4/22/19



4/24/19





Gene Trails/MATCH NSG Results



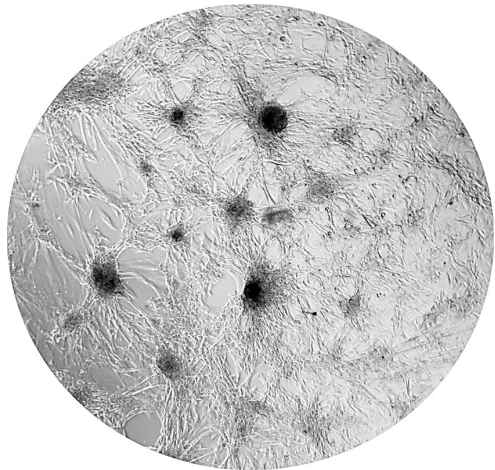
- Positive for **MYOD1 p.L122R**
- Positive for **PIK3CA p.I459_T462del**
 - In-frame deletion of the PIK3CA gene has not been characterized
 - Involves area of exon 9 (commonly mutated, leading to activation of PI3 kinase signaling)
 - In spindle cell rhabdomyosarcomas, PIK3CA mutations have been reported in association with the above MYOD1 mutation
- Positive for **PTEN p.R173H**
- Positive for **GNAS p.R201C**
- The MATCH trial identified LY compound LY3023414 (dual PI3KCA and mTOR inhibitor) if his tumor were to recur.



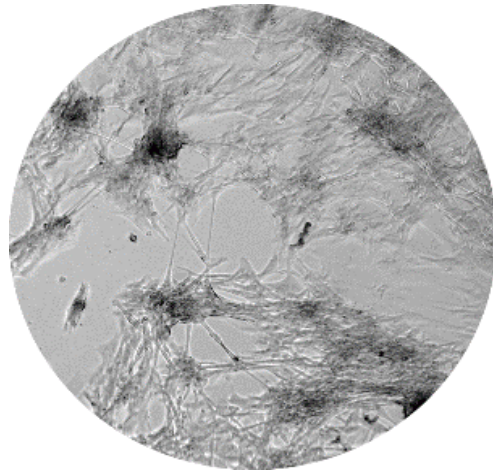
SARC001



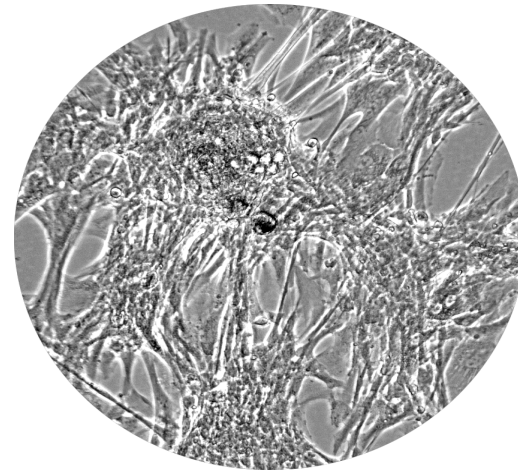
- First patient derived cell line with a MyoD1 mutation in spindle cell rhabdomyosarcoma with a PI3KCA p.I459_T462del (exon 9)



2x

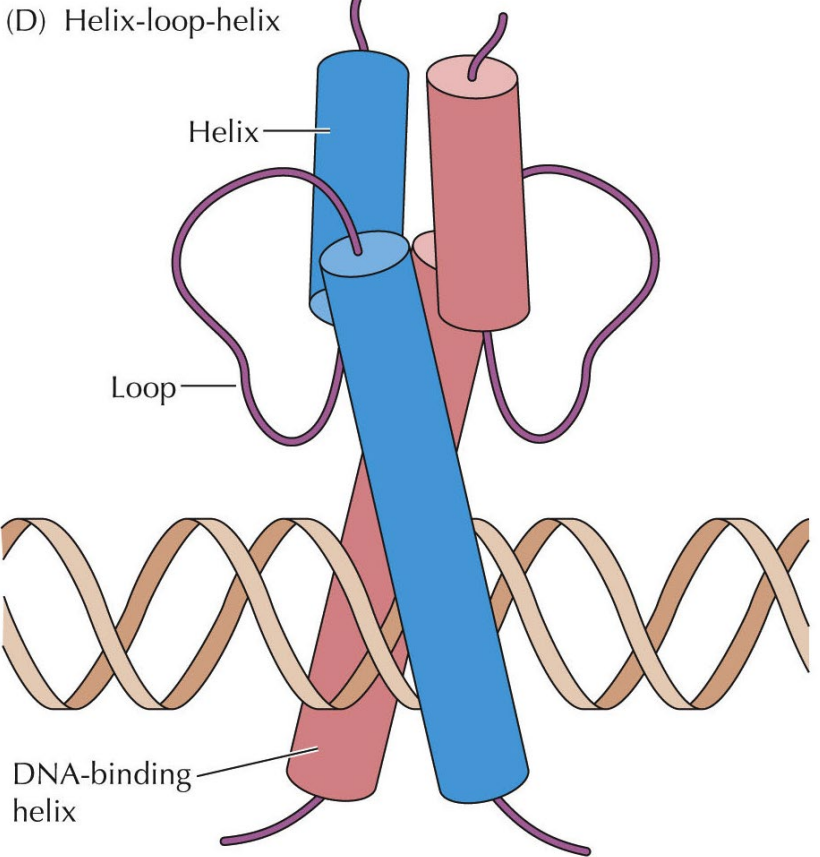
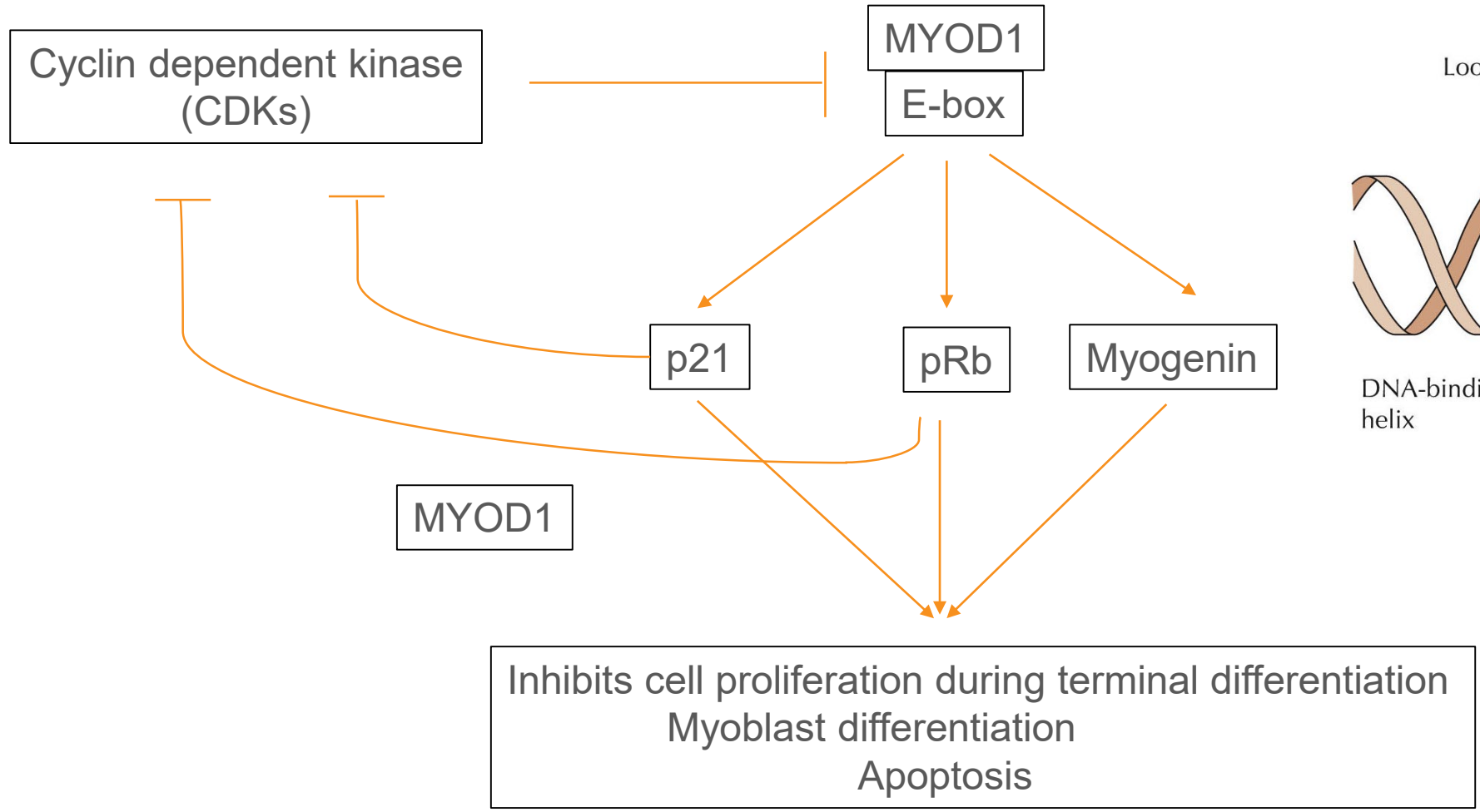


4x



10x

+ Function of MYOD1

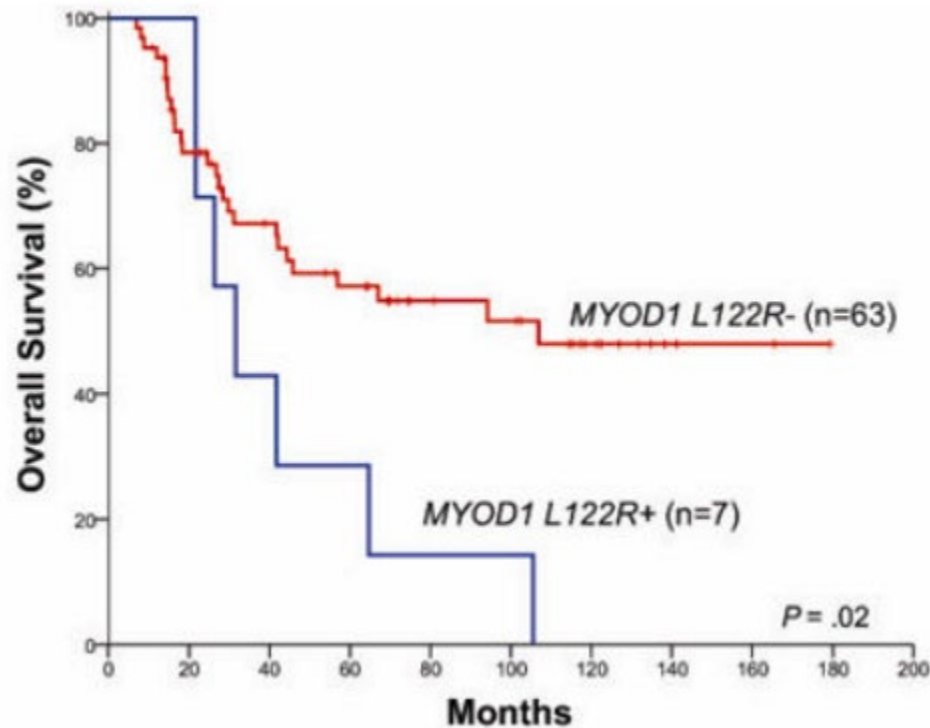




MYOD1 Mutations in Spindle Cell Rhabdomyosarcoma



- Leu122Ar substitution mutation
 - Competes for binding site of WT MYOD1 = blocks differentiation
 - Also competes for binding site of MYC= induces proliferation

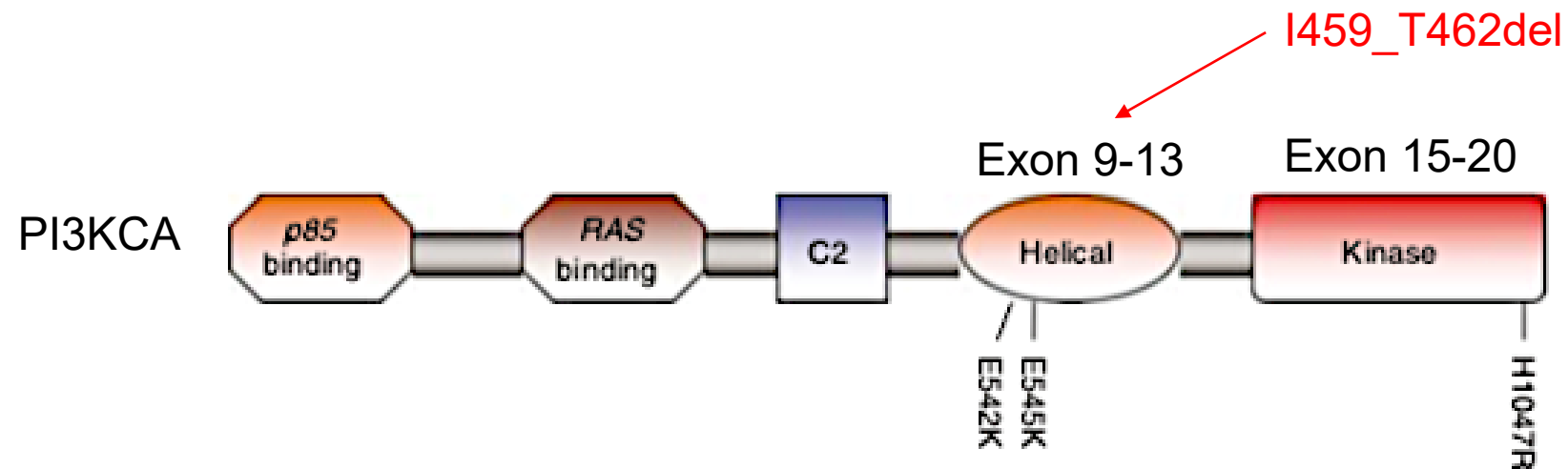




PI3KCA Mutations in Spindle Cell Rhabdomyosarcoma



- Somatic missense mutation hot spots found in exon 9 and 20. (G1624A:E542K)
 - H1047R
 - E542K
 - E545K
- Oncogenic



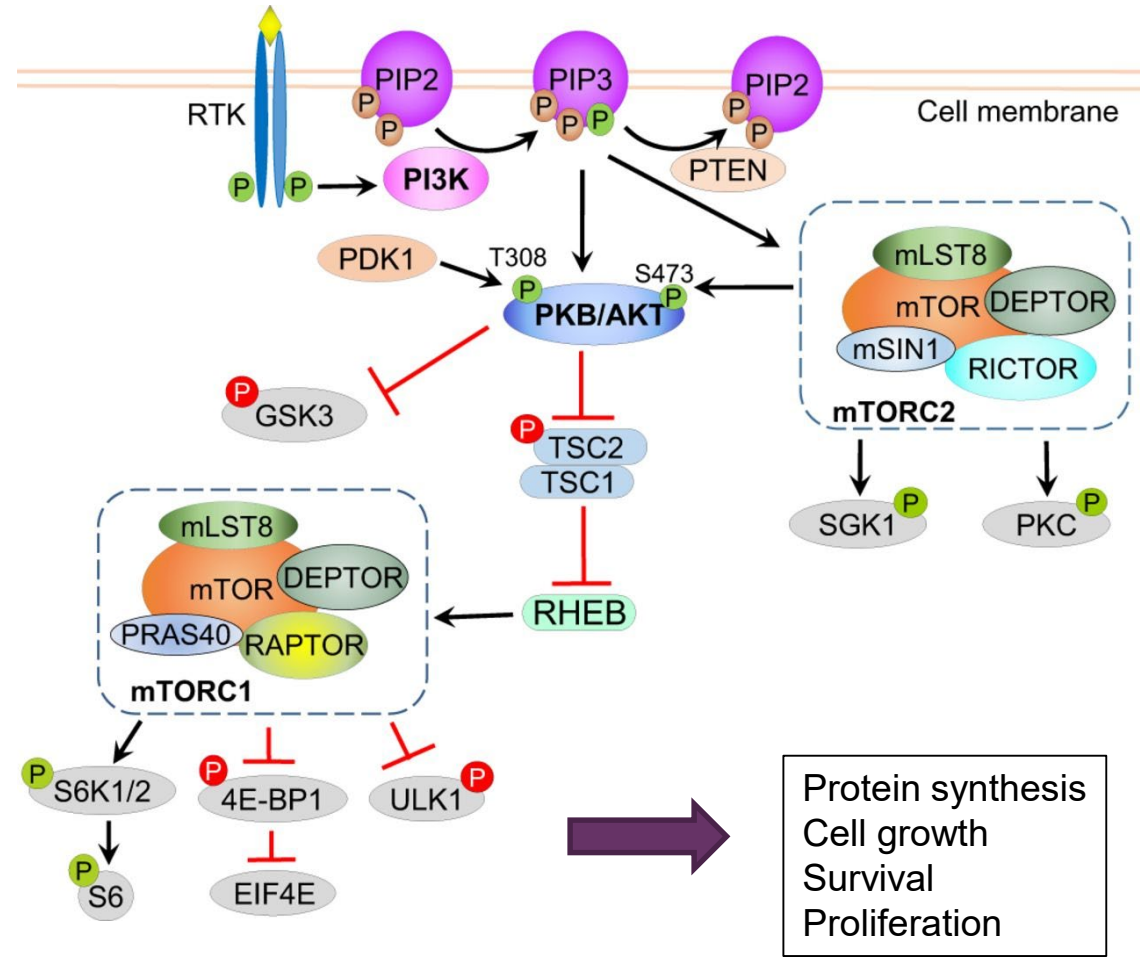
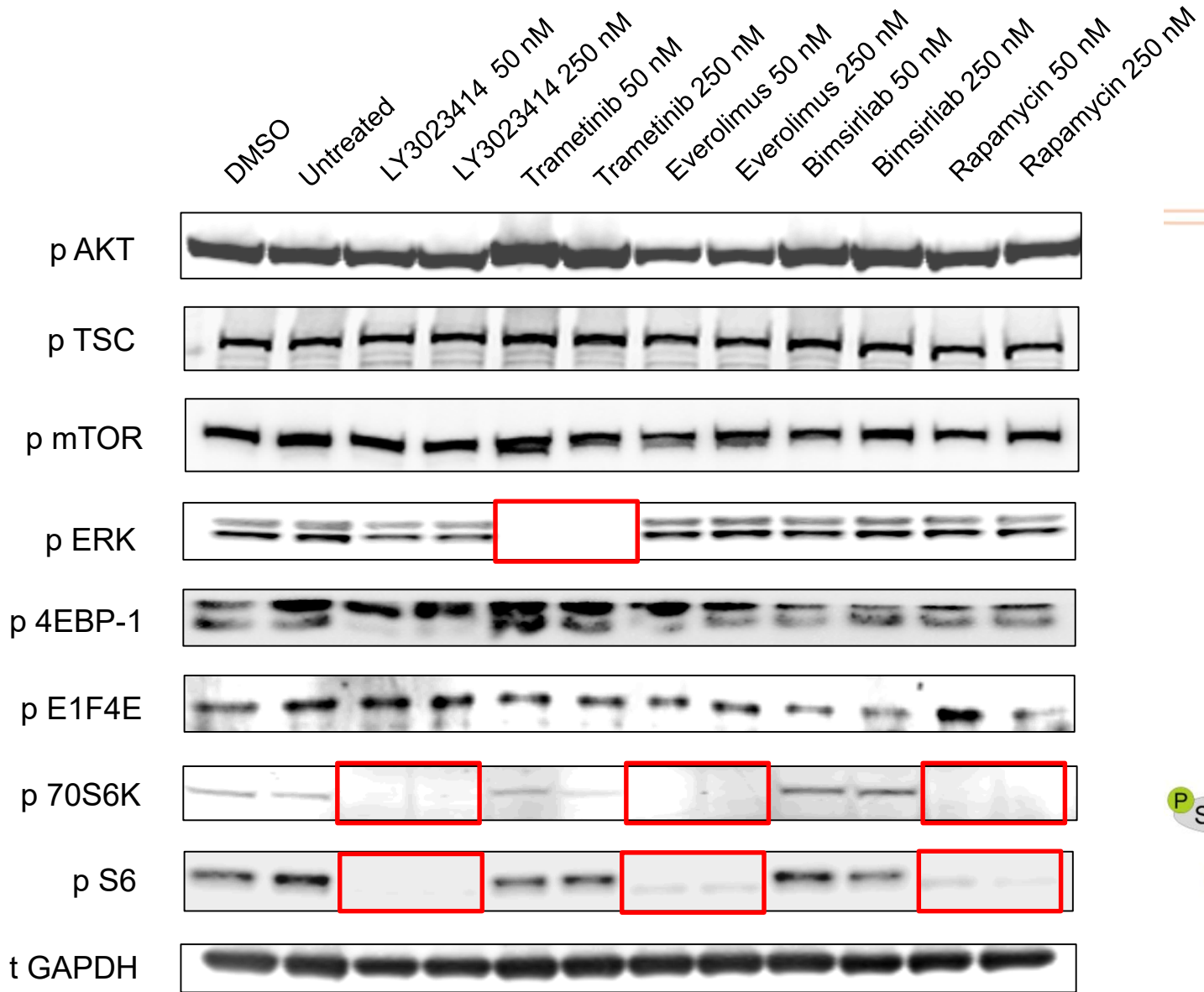


GNAS in Spindle Cell Rhabdomyosarcoma



- Role of MAPK/GNAS pathway unknown in spindle cell rhabdomyosarcoma

+ Signaling Changes in Drug Treated SARCO01

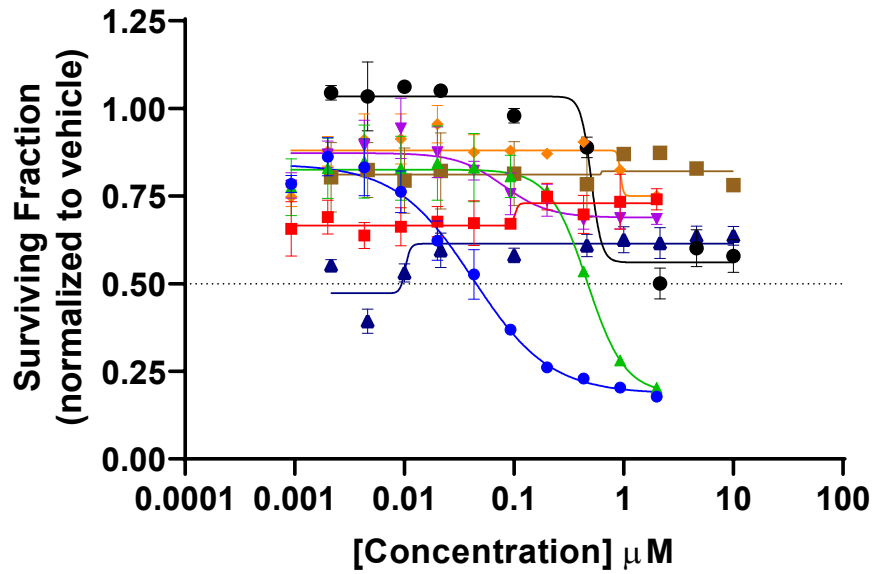




Drug Dose Response Curves

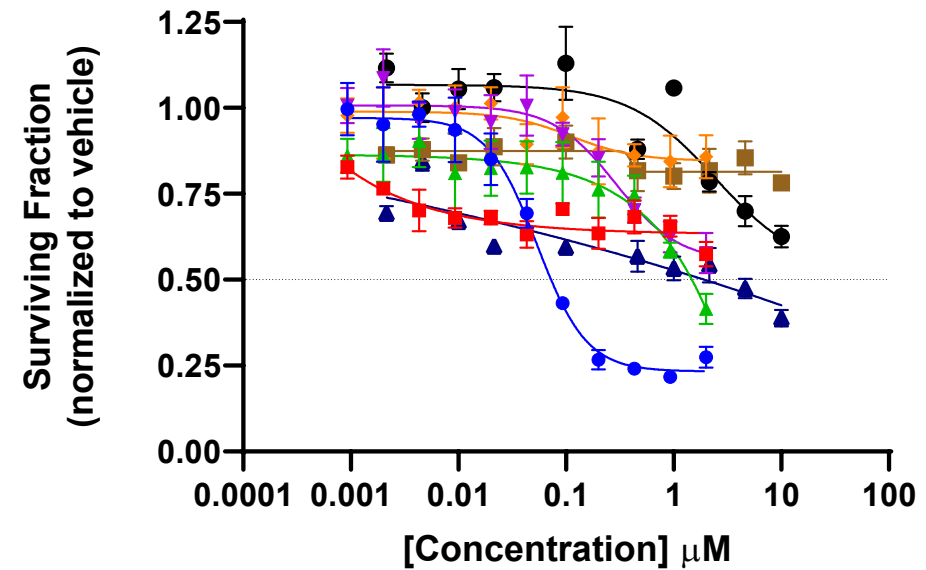


SARC001 3000 cells, 3.0 hr



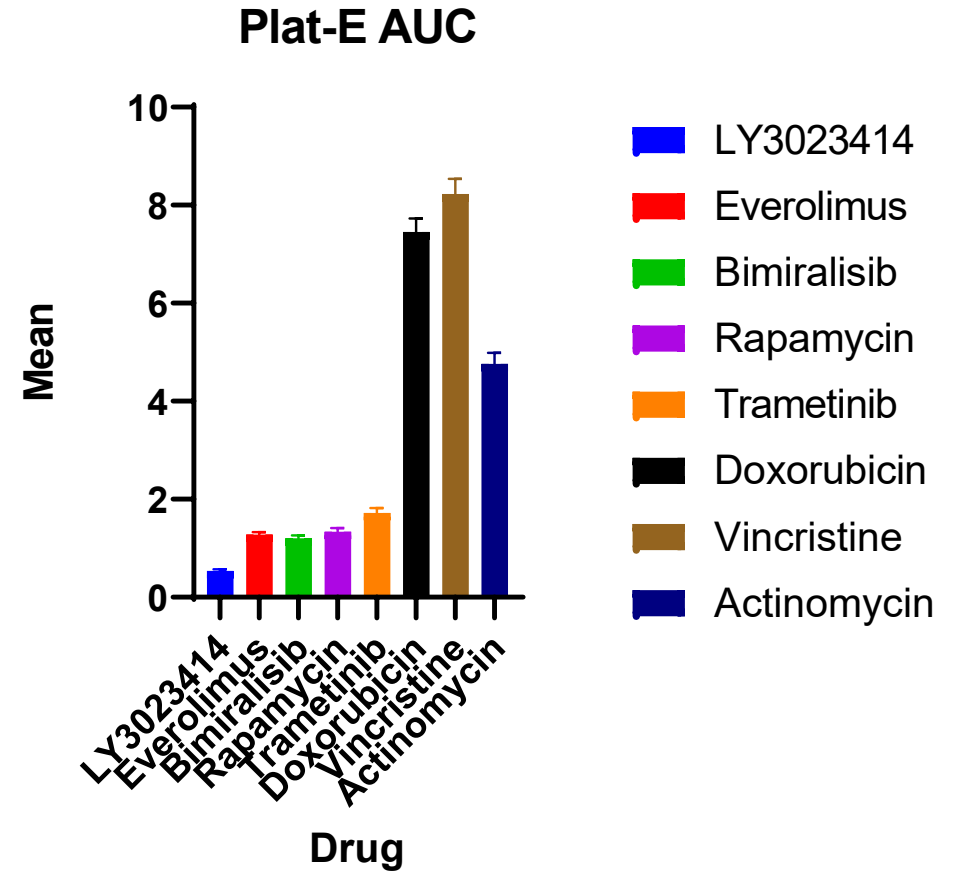
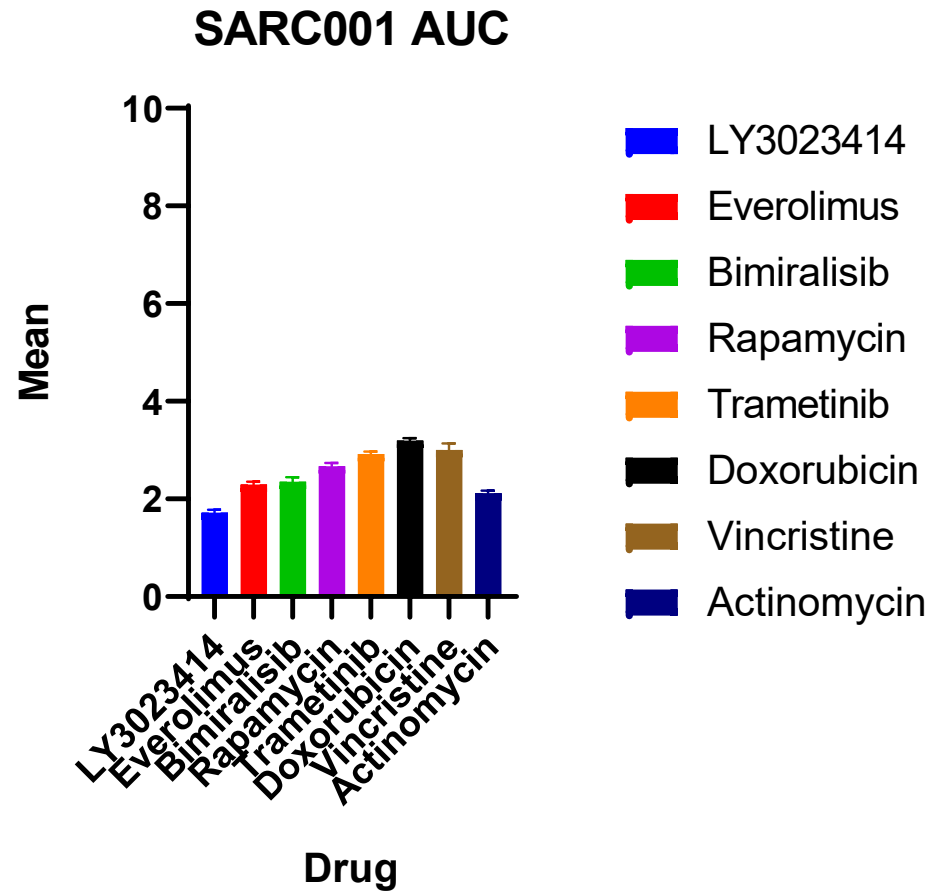
- LY3023414
- Everolimus
- Bimiralisib
- Rapamycin
- Trametinib
- Doxorubicin
- Vincristine
- Actinomycin

Plat-E 1000 cells, 4 hr



- LY3023414
- Everolimus
- Bimiralisib
- Rapamycin
- Trametinib
- Doxorubicin
- Vincristine
- Actinomycin

Drug Dose Response- Area Under Curve





Conclusions



- LY3023414 significantly inhibited SARC001 cell viability but appears to have significant cell toxicity. SARC001 refractory to single agents
- Potential roles of multiple agent chemotherapies
- Downstream effectors in the PIK3CA/AKT pathway (pS6 and p70S6K) were significantly downregulated after LY3023414, everolimus, and rapamycin treatments
- Ongoing studies include investigating tumorigenicity and inhibitor-responses of SARC001 in vivo and characterizing the role of PIK3CA deletion and GNAS in signaling pathways using site directed mutagenesis.
- Our results demonstrate the importance of patient-derived models, particularly in rare cancers such as SCR, for assessing preclinical efficacy of molecularly-targeted treatments



Thank you!



Mentors

Monika Davare, PhD

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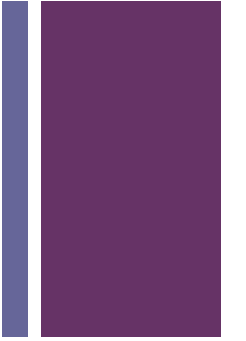
Kevin Nusser, PhD

Sudarshan Iyer

OHSU biolibrary

Patient and his family





Questions?