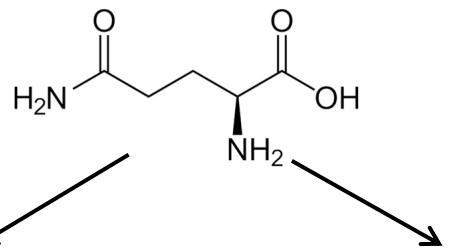
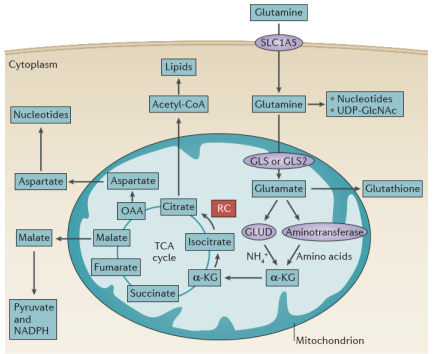
Glutamine Transporter as an Anti-Neoplastic Drug Target

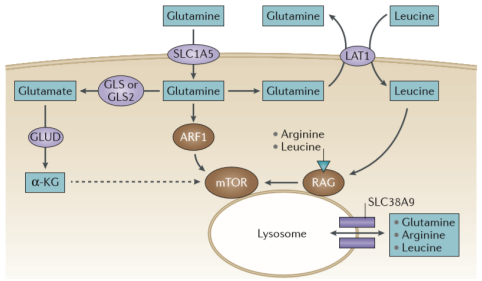
glutamine



Mitochondrial Role (metabolic)

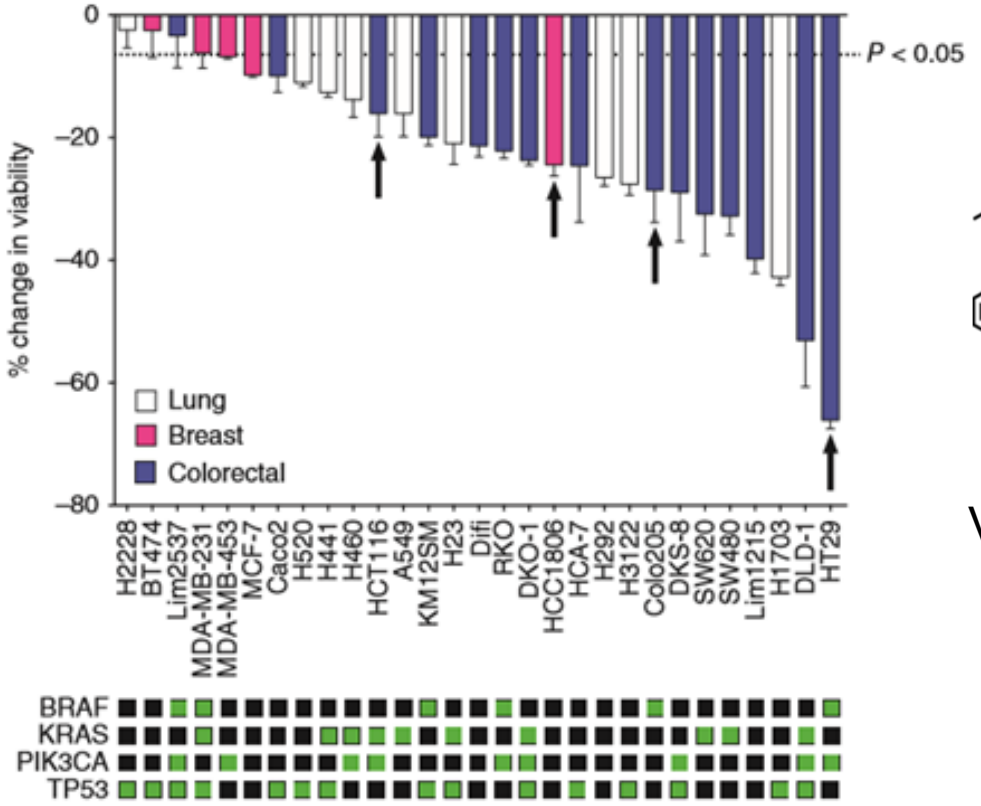


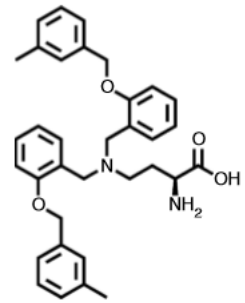
Extra-Mitochondrial Role (signal transduction)



While glutaminase inhibitors (currently in clinical trials) target the mitochondrial role of glutamine, glutamine transport inhibitors also harness the extra-mitochondrial role of glutamine within cell to inhibit proliferation

V-9302 is a novel inhibitor of glutamine transporter ASCT2/SCL1A5 that has shown *in vitro* and *in vivo* efficacy in lung, breast and colorectal cancer cell lines





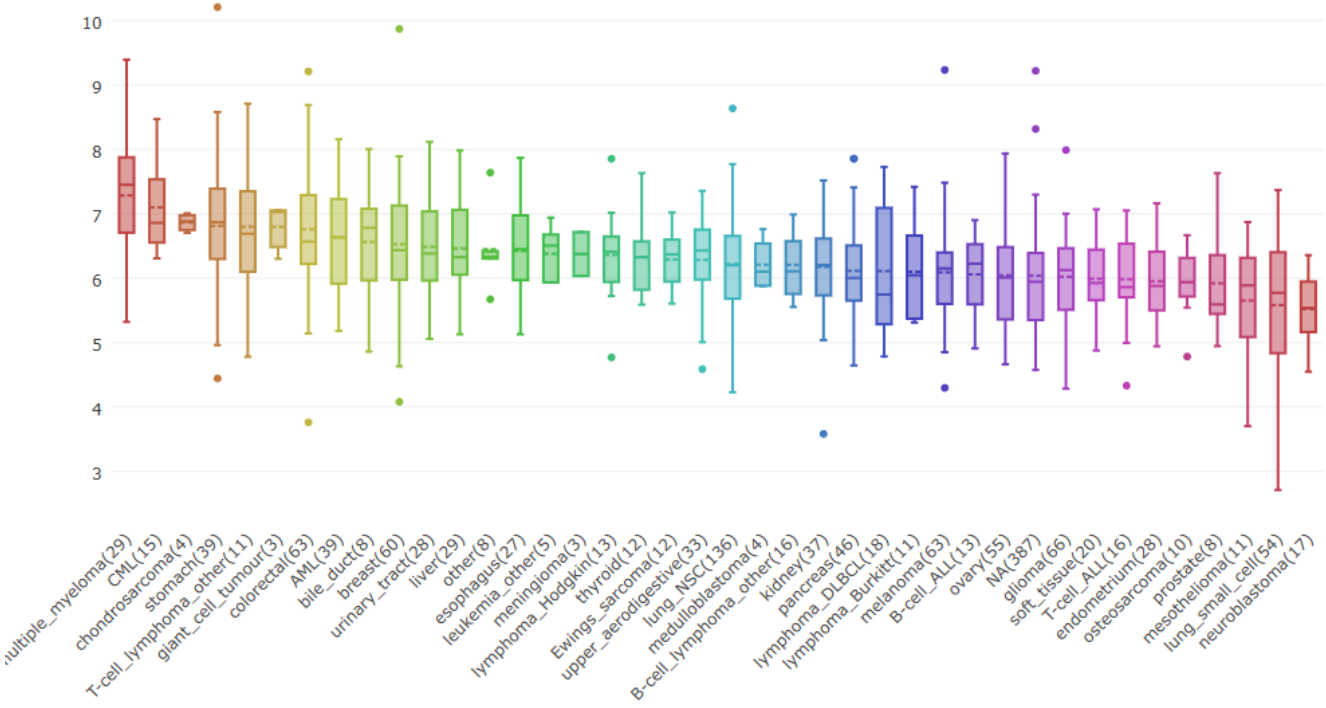
V-9302

Altman et al *Nat Reviews* 2016

Schulte et al *Nat Med* 2017

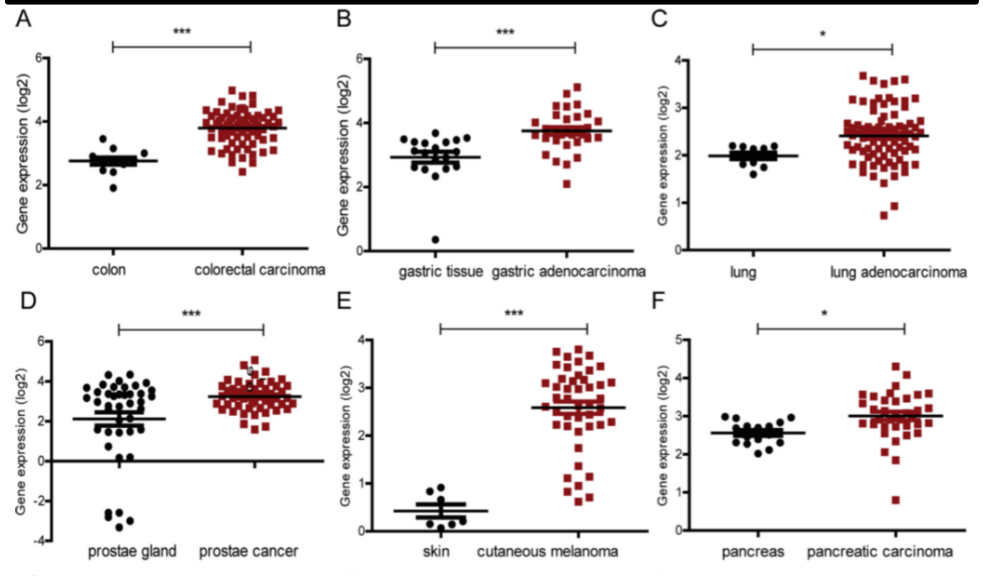
Glutamine Transporter ASCT2 in Cancer

ASCT2 Expression is Upregulated in Diverse Cancer Cell Lines

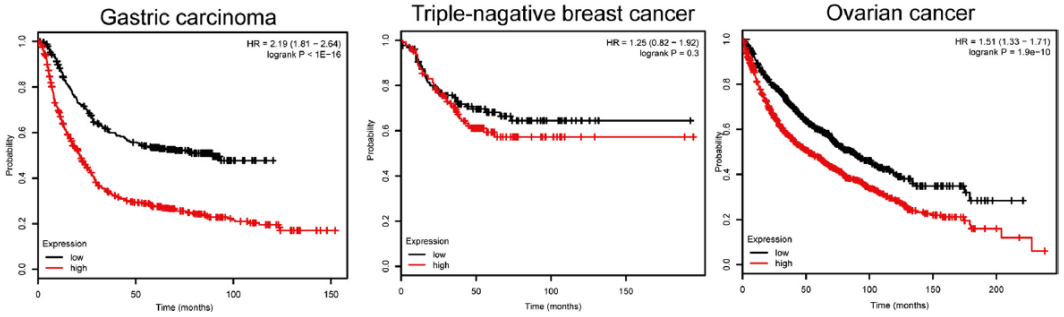


Liu et al 2018
CCLE (Broad Institute)

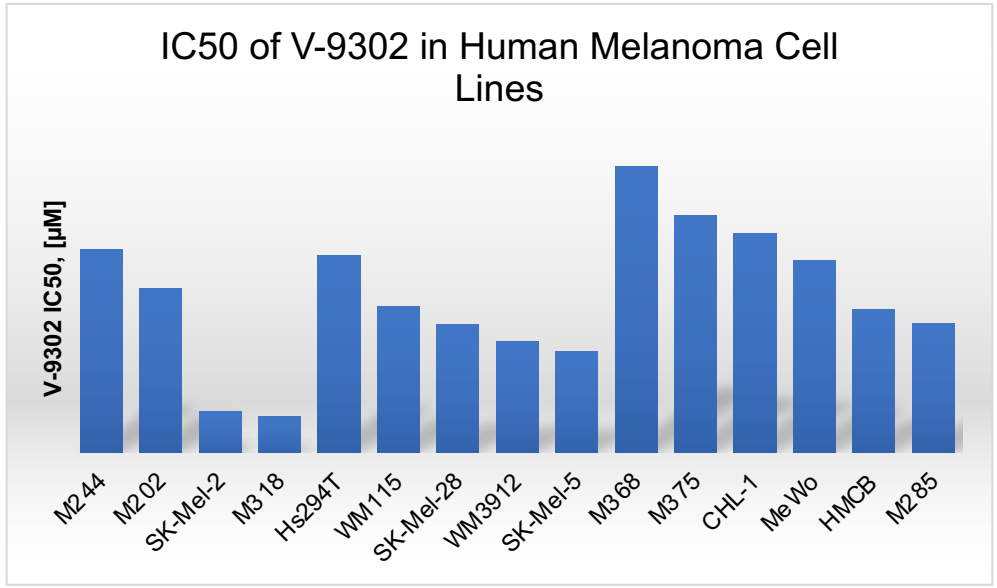
ASCT2 expression is increased in malignant tissue as compared to normal tissue

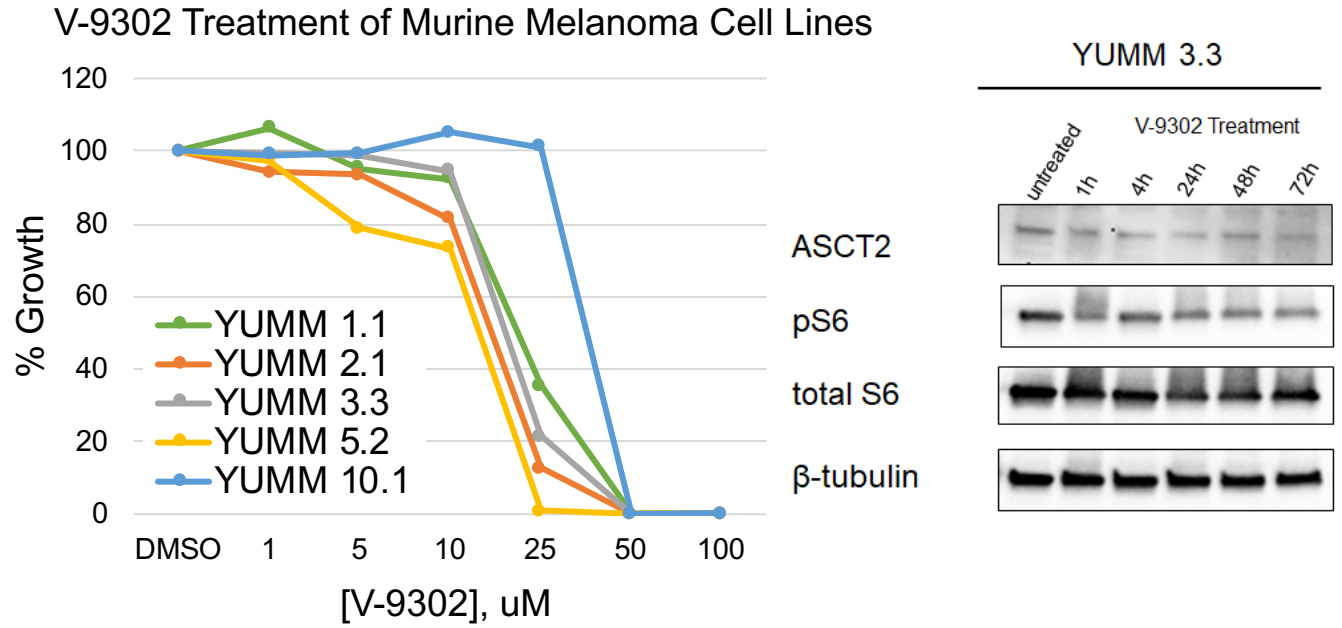


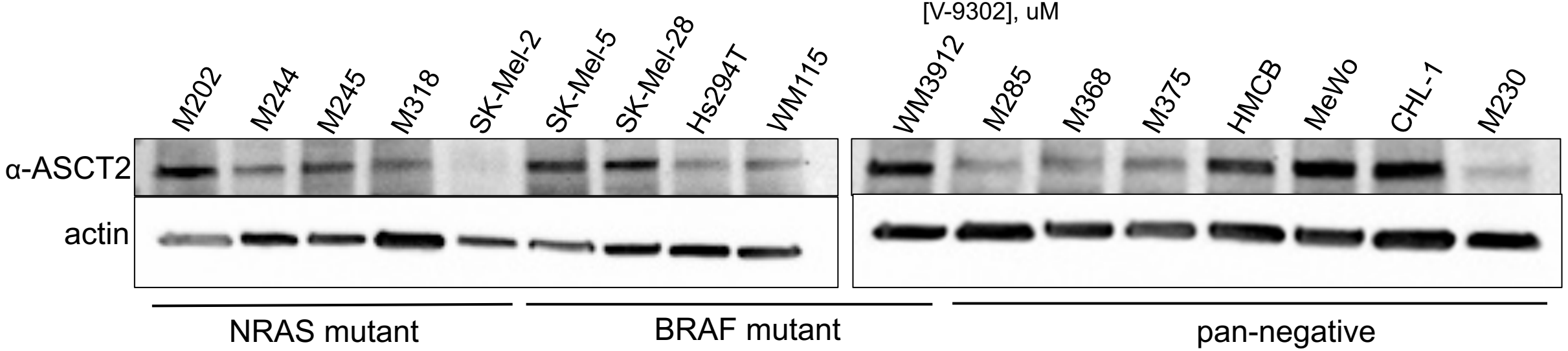
Elevated ASCT2 Expression Correlates with Poor Survival



Glutamine Transporter Inhibitor V-9302 Inhibits *in vitro* Melanoma Cell Growth

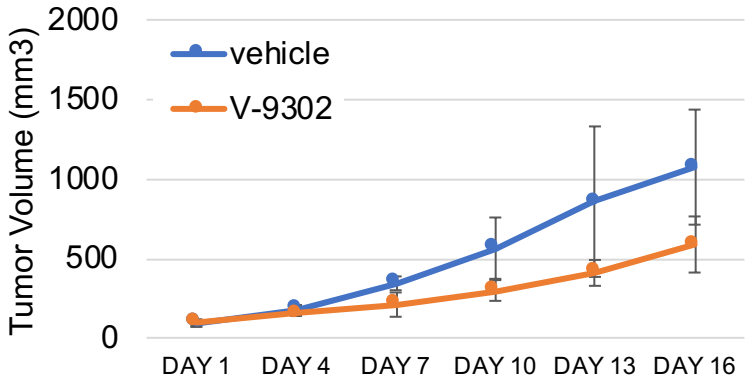




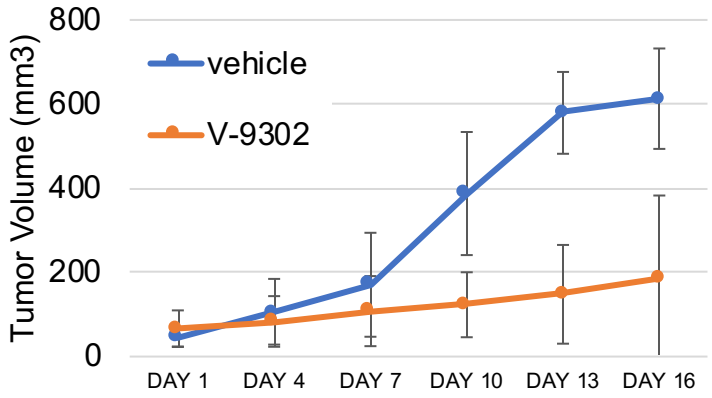


Glutamine Transporter Inhibitor V-9302 Inhibits *in vivo* Melanoma Cell Growth

YUMM 3.3 xenograft model

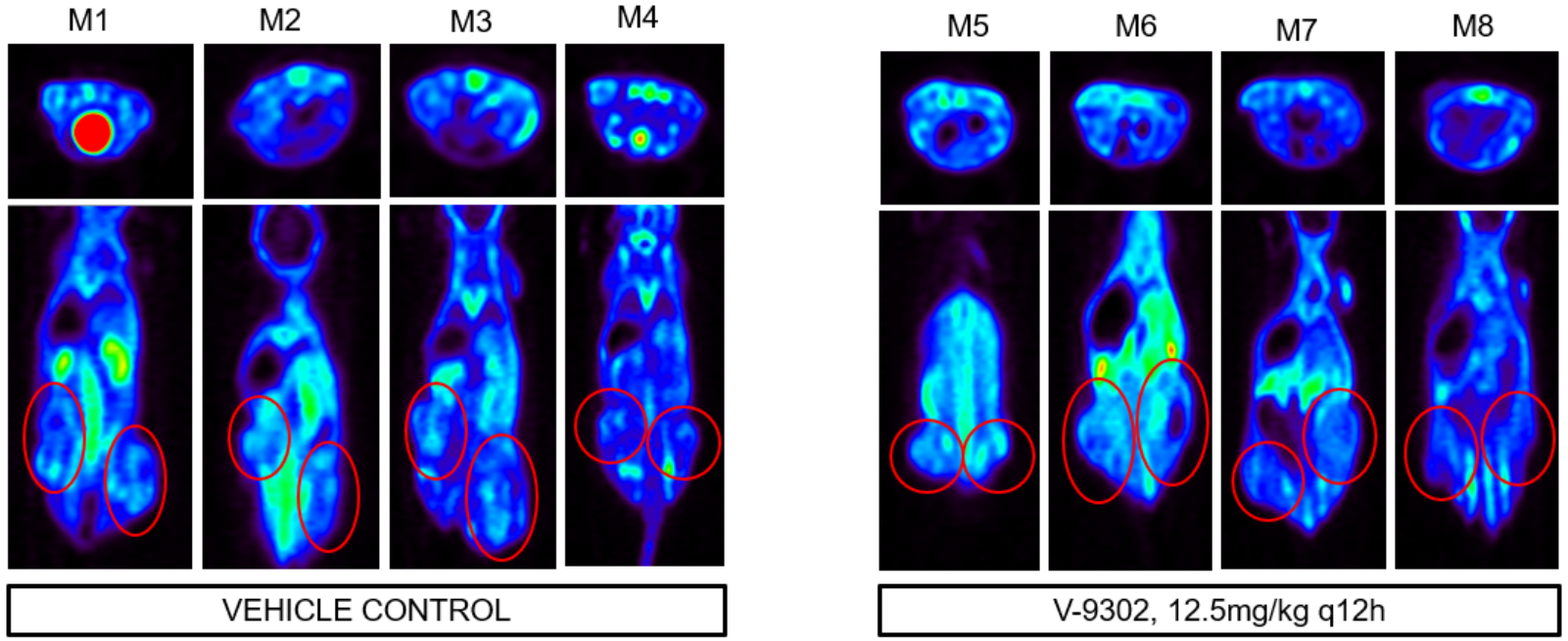


YUMM 5.2 xenograft model



- V-9302 treatment significantly reduces YUMM 5.2 melanoma xenograft tumor growth in vivo with minimal toxicity
  - Primary toxicity observed: weight loss

18F-glutamine imaging in control and V-9302-treated mice



Conclusions and Future Directions: Glutamine Transporter Inhibitor V-9302 in Melanoma

CONCLUSIONS

- The glutamine transporter represents a novel drug target with great potential for both diagnostic and therapeutic applications.
  - Diagnostic: F18-glutamine PET imaging
  - Therapeutic: glutamine transport inhibitors, such as V-9302, currently in pre-clinical development
- V-9302 inhibits melanoma tumor cell growth *in vivo* and *in vitro*

FUTURE DIRECTIONS

- Given the clinical efficacy of immune checkpoint inhibitors in melanoma, we will evaluate the combination of V-9302 plus anti-PD-1/L1 in vivo
  - Theoretical basis: tumor cells rely more heavily on glutamine metabolism than immune cells, which are glucose-dependent. Targeting glutamine transport will preferentially effect tumor cells, while PD-1/L1 inhibition will induce immune activation
  - *In vivo* experiment pending