In Pre-clinical Models Metabolic Manipulations Improve the Efficacy of T Cell Immunotherapy of Melanoma

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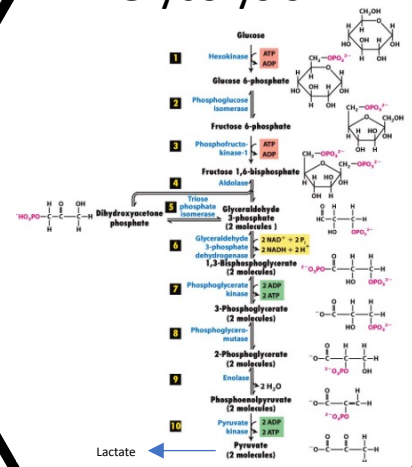
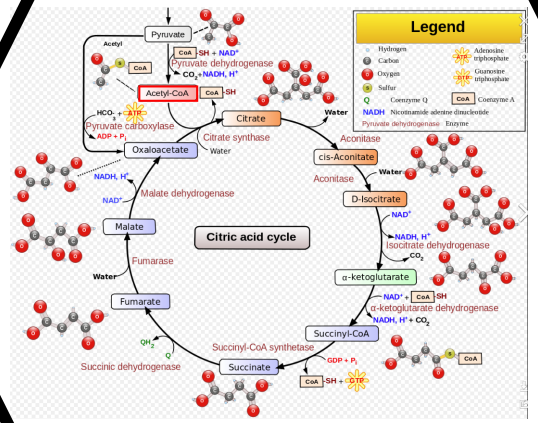
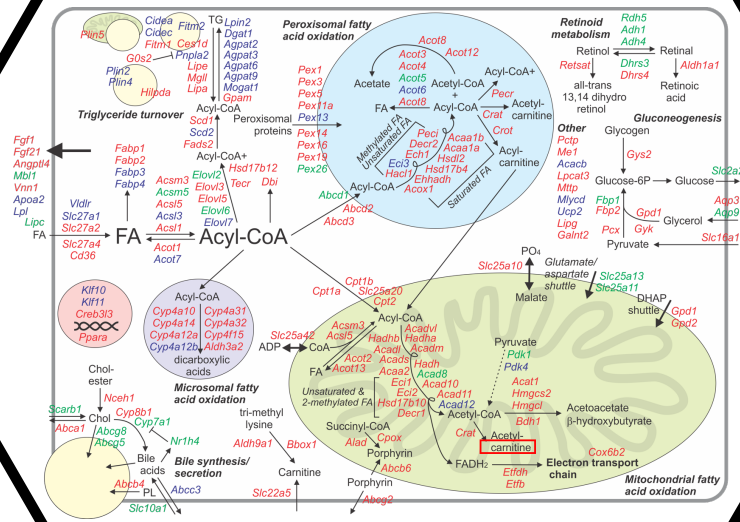
Glycolysis



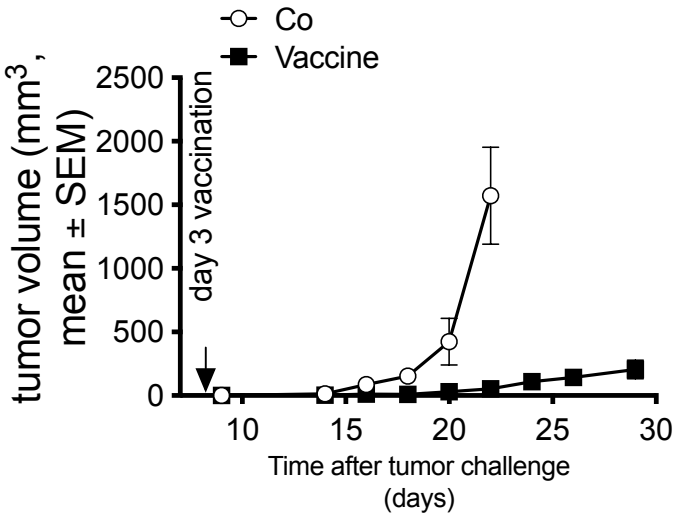
TCA cycle

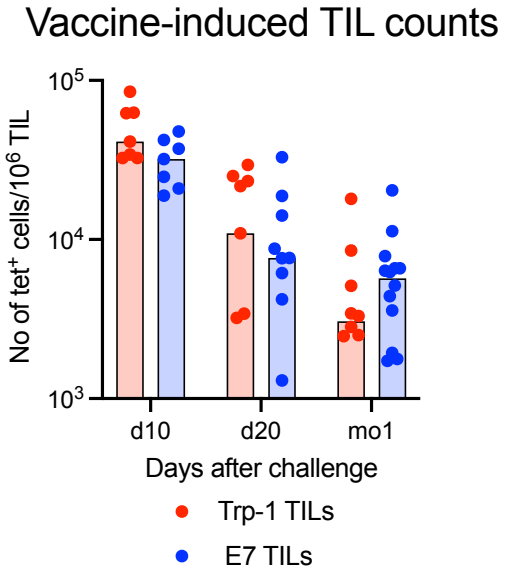


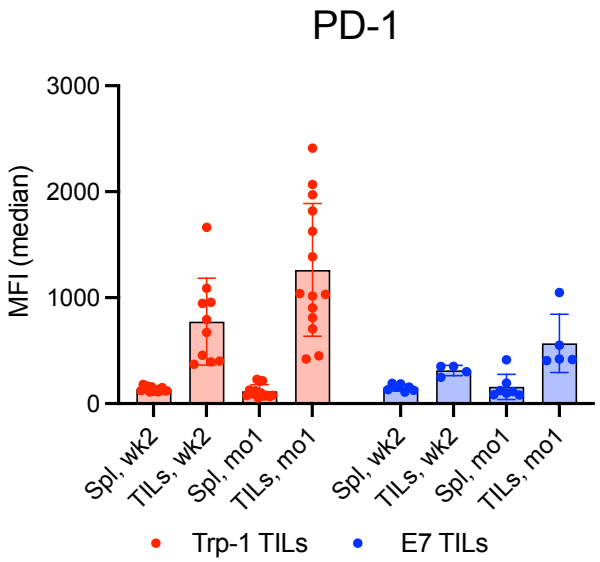
Fatty acid metabolism

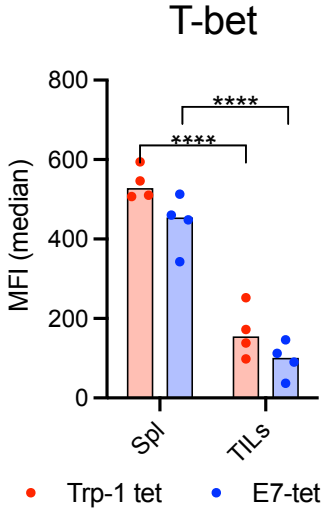


$CD8^+$ TILs become impaired during tumor progression

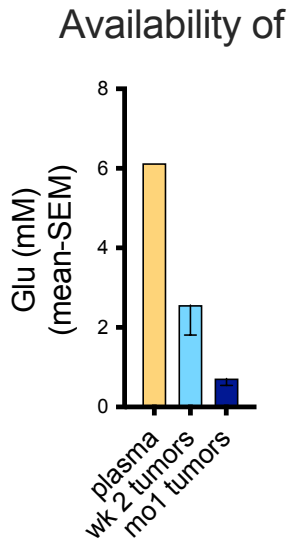


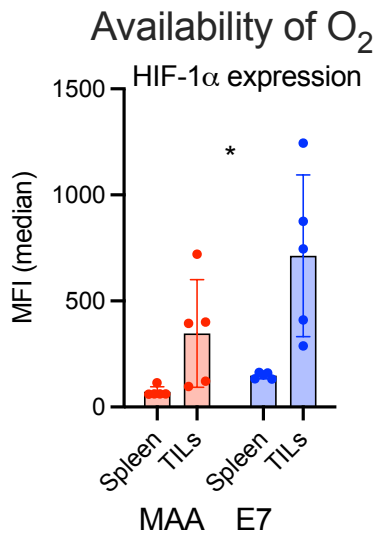




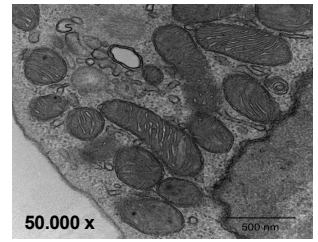


Lack of Glucose and O_2 causes metabolic stress of $CD8^+$ T cells

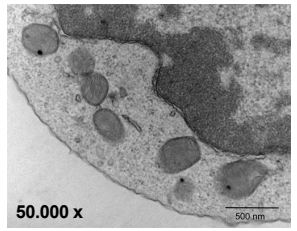


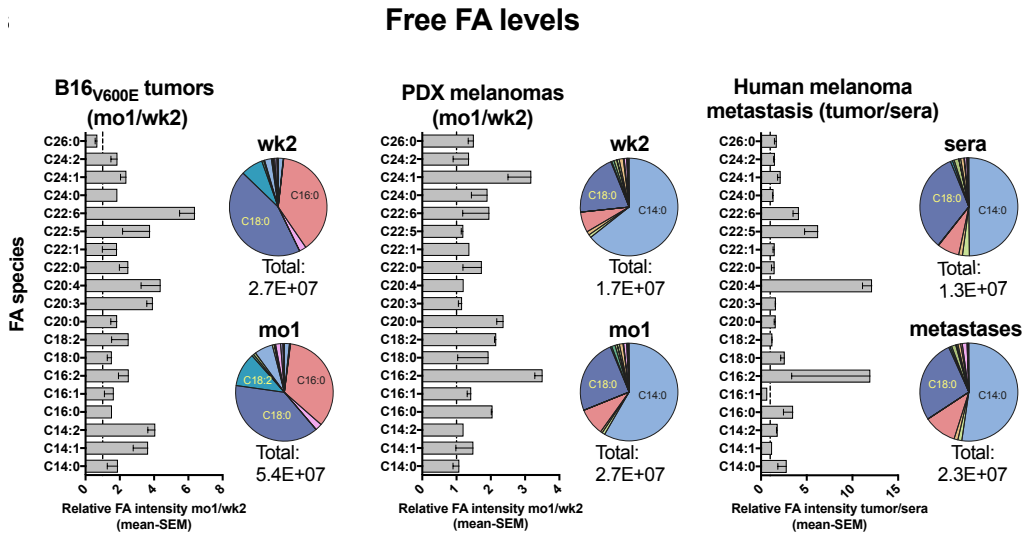


$CD8^+$ T cells
Spleen

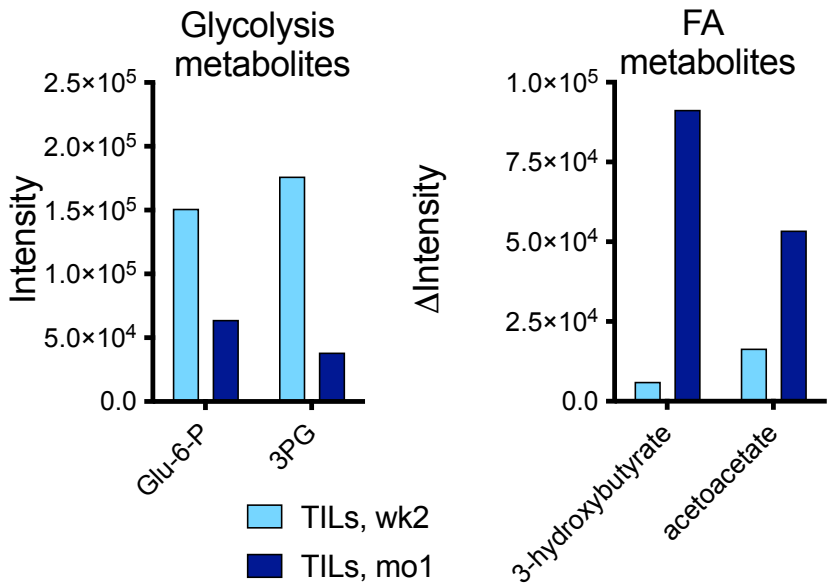


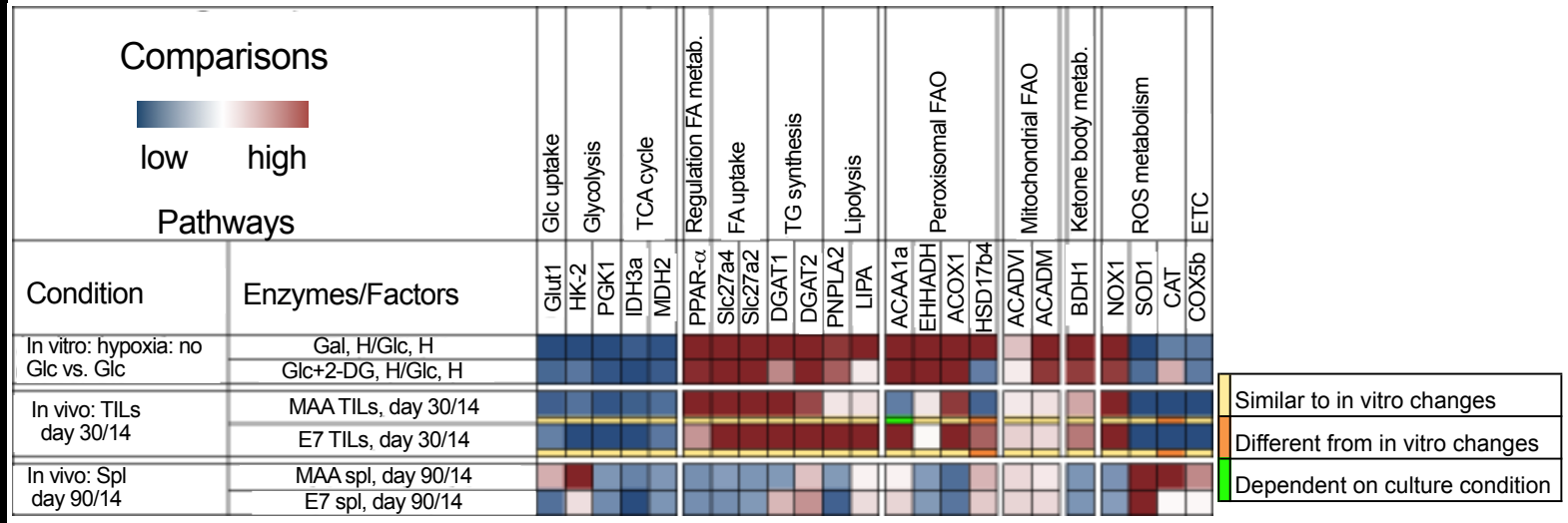
Tumor





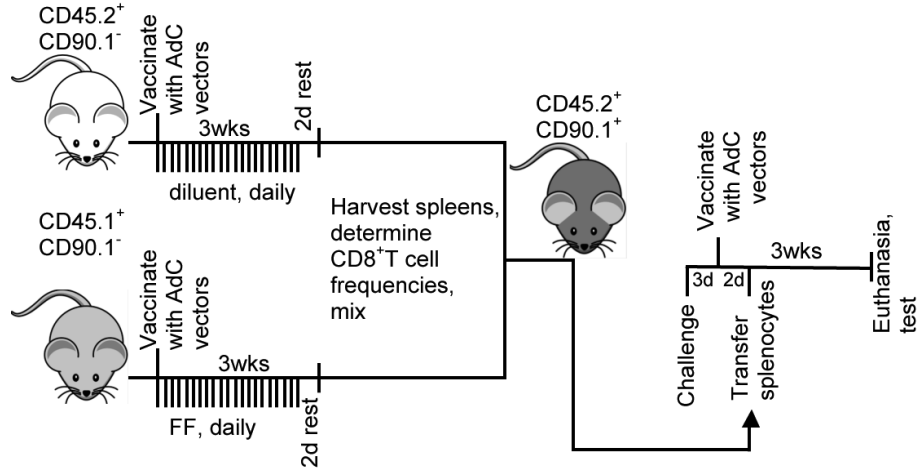
Hypoglycemia combined with hypoxia prompts CD8+ T cells to switch from glycolysis to fatty acid catabolism

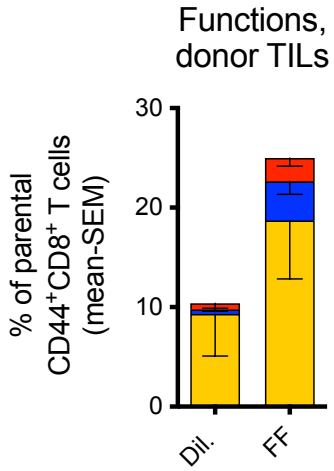


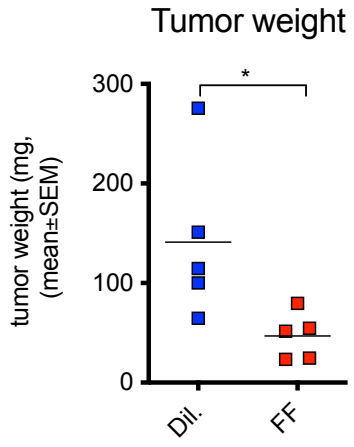


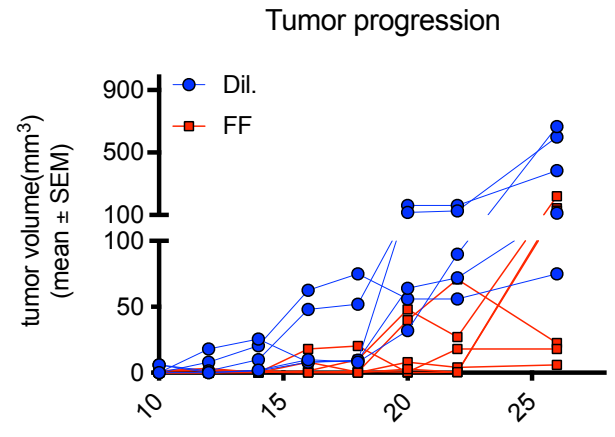
In a mouse melanoma model drug-induced increases in fatty acid metabolism increases the efficacy of adoptively transferred melanoma-specific T cells

FF-fenofibrate, a PPARα agonist

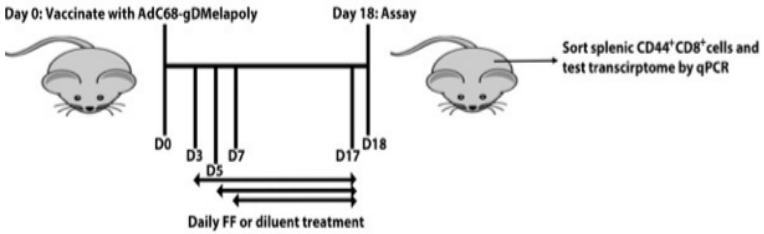


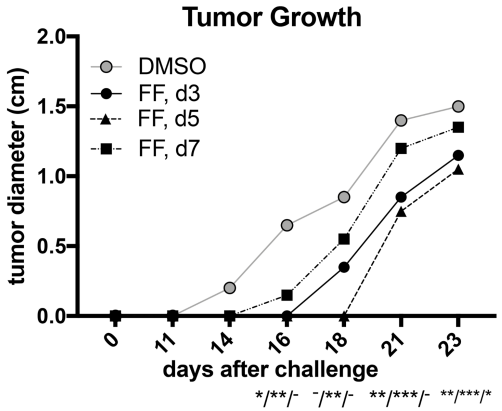


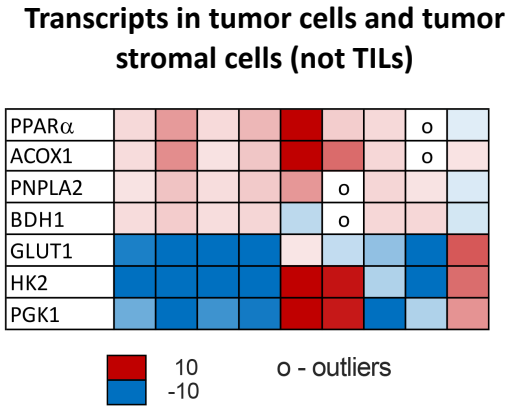


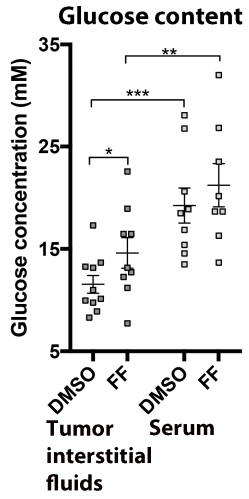


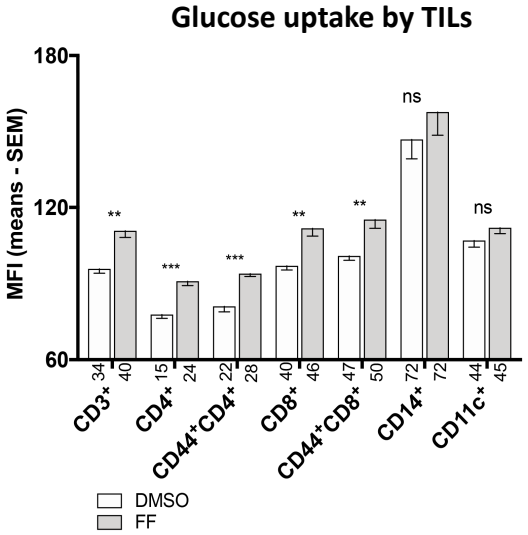
In a mouse model of melanoma increasing fatty acid metabolism increases vaccine efficacy





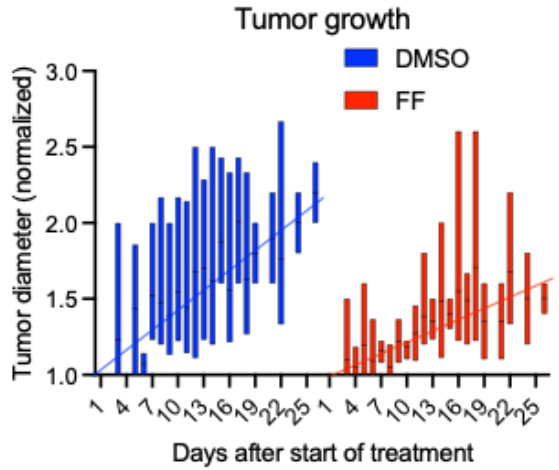


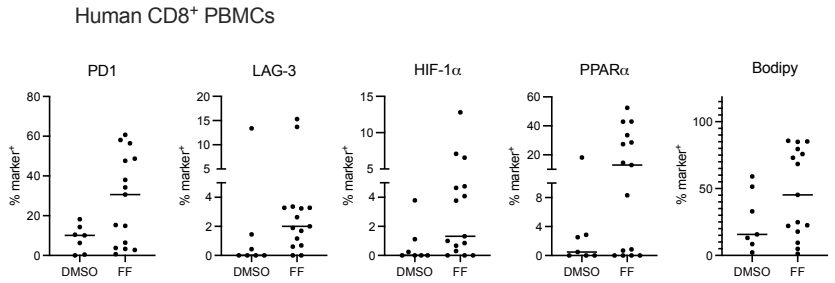


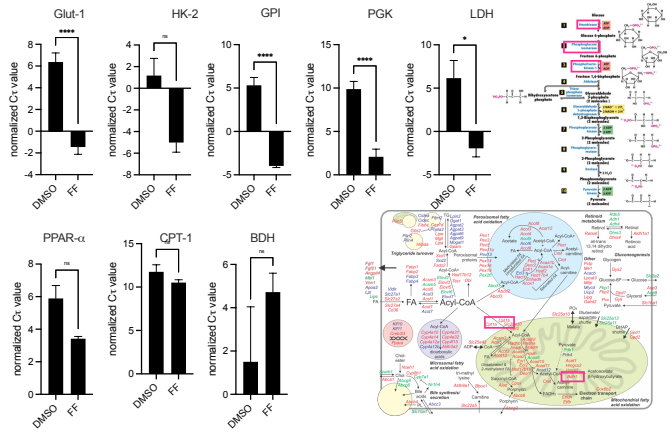


NSG model with fresh human melanoma fragments

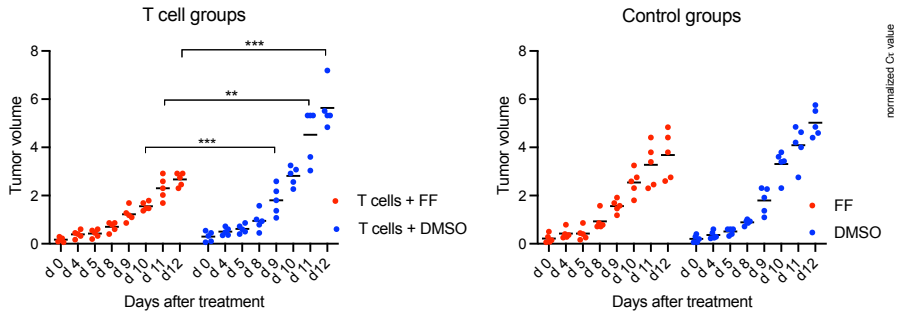
2 recurrent melanomas,
1 metastatic melanoma,
1 primary melanoma







Metastatic Melanoma



Summary: A PPAR-α agonist can improve fitness of TILs through two mechanisms

1) In an adoptive transfer mouse model training tumor antigen-specific T cells prior to transfer to switch to fatty acid metabolism increases their fitness within the TME by increasing their catabolism of fatty acids
2) In tumor bearing, vaccinated mice treatment with a PPAR-α agonist induces tumor cells to switch to fatty acid metabolism thus increasing the availability of glucose for TILs, which again increases their fitness
3) In an adoptive model based on human tumors transplanted into NSG mice that in addition received autologous TILs a PPAR-α agonist given to the mice affects tumor cells rather than TILs (see 2 above)
4) No yet tested: Treatment of TILs prior to transfer

Acknowledgements and Disclosures

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