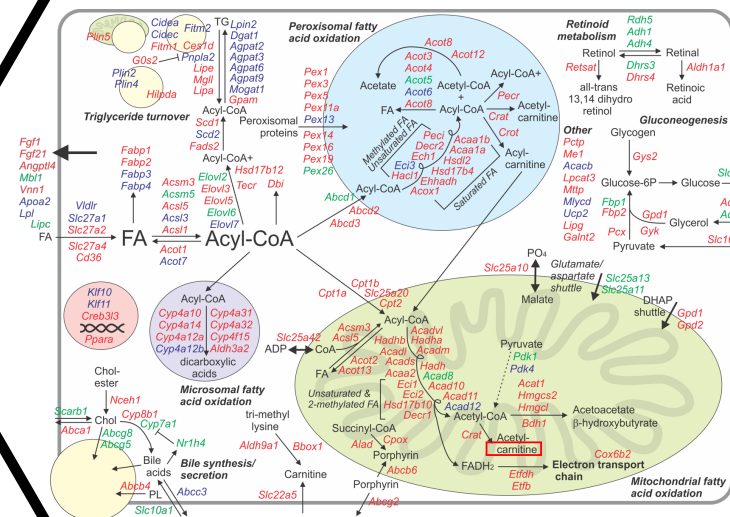
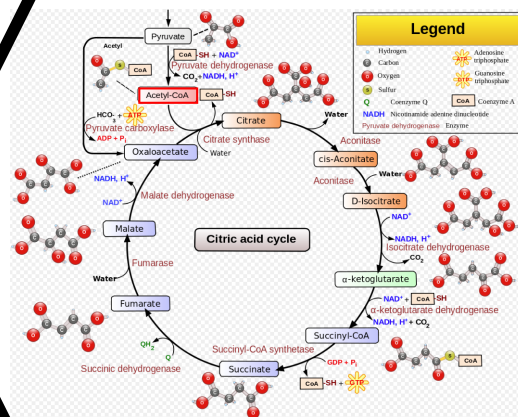
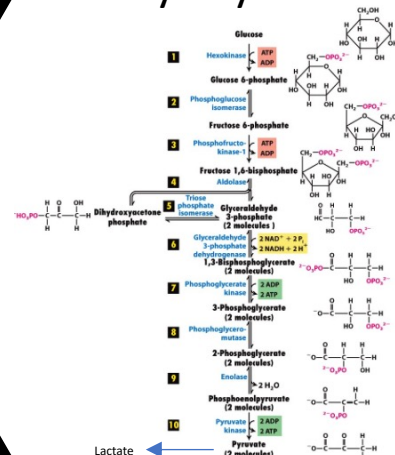
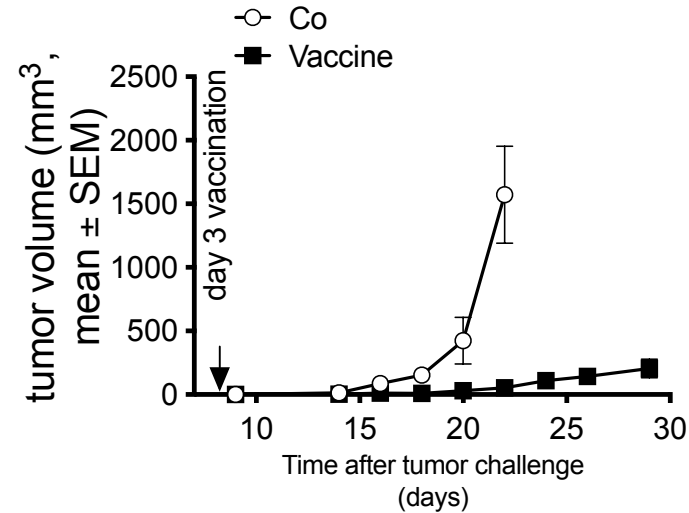


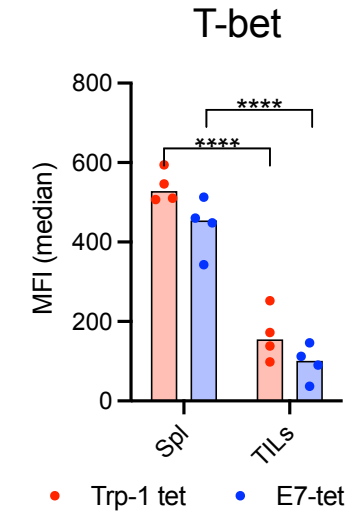
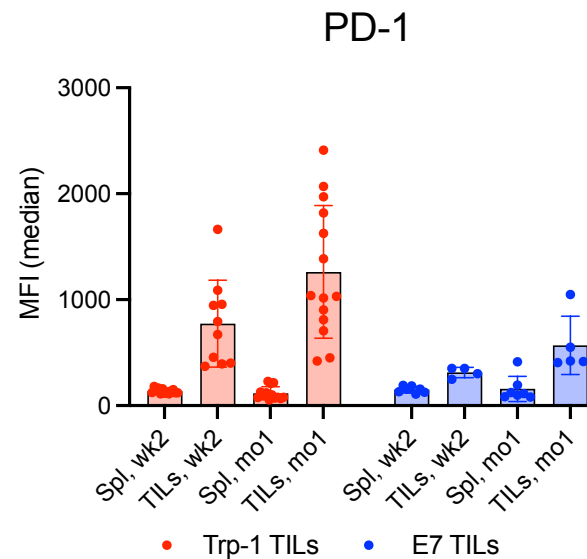
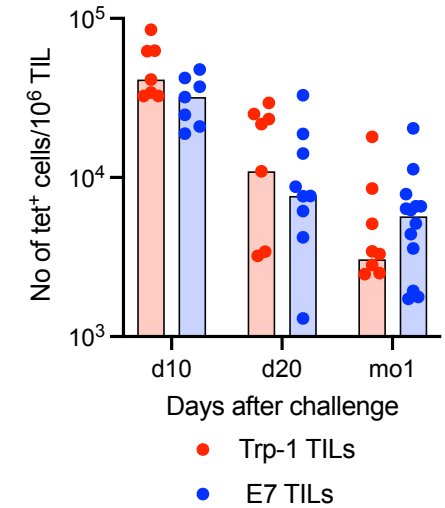
H. Ertl
Wistar Institute
Philadelphia, PA

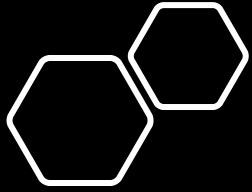


CD8⁺ TILs
become
impaired during
tumor
progression

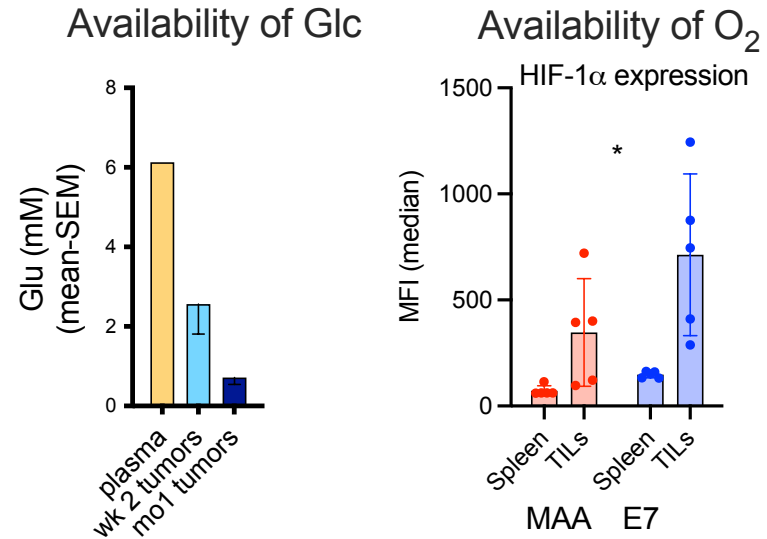


Vaccine-induced TIL counts

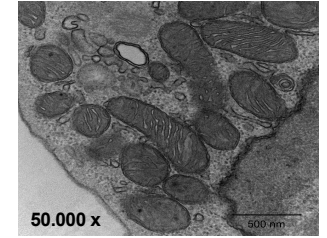




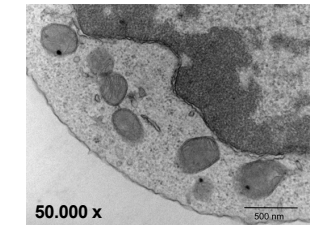
Lack of Glucose
and O₂ causes
metabolic stress
of CD8⁺ T cells



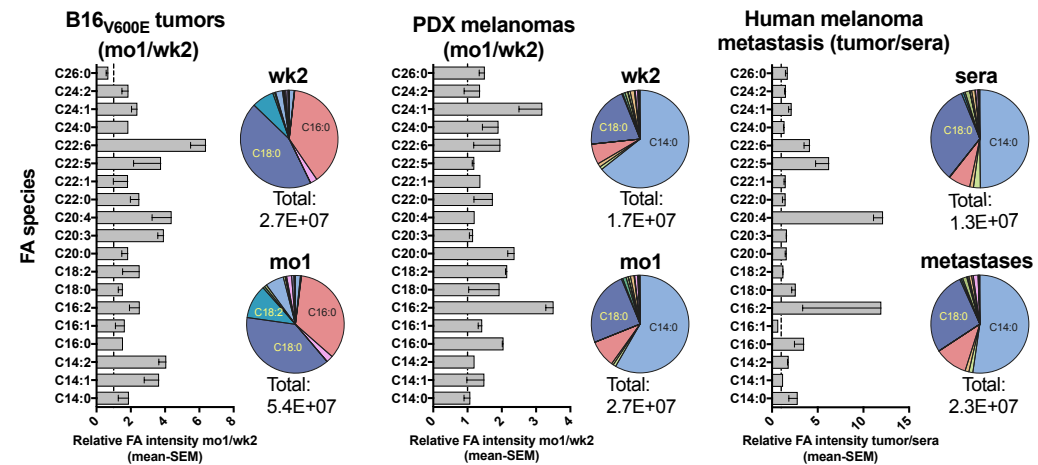
CD8⁺ T cells
Spleen

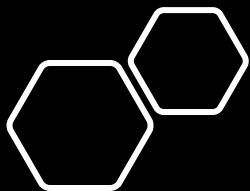


Tumor

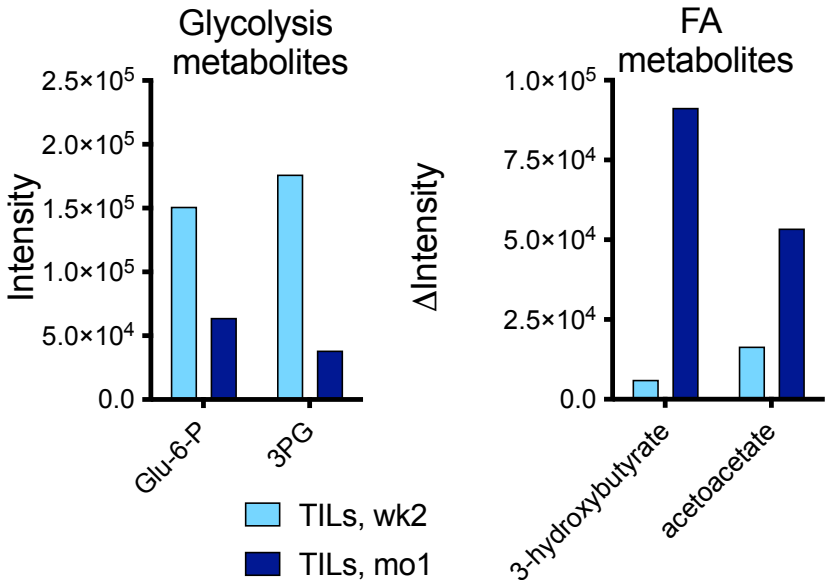


Free FA levels





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

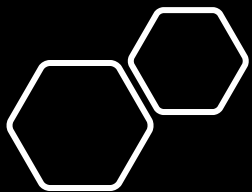


Comparisons		Pathways																											
		Glc uptake					Glycolysis		TCA cycle		Regulation FA metab.		FA uptake		TG synthesis		Lipolysis		Peroxisomal FAO		Mitochondrial FAO		Ketone body metab.		ROS metabolism		ETC		
Condition	Enzymes/Factors	Glut1	HK-2	PGK1	IDH3a	MDH2	PPAR-α	Slc27a4	Slc27a2	DGAT1	DGAT2	PNPLA2	LIPA	ACAA1a	EHHADH	ACOX1	HSD17b4	ACADV1	ACADM	BDH1	NOX1	SOD1	CAT	COX5b					
In vitro: hypoxia: no Glc vs. Glc	Gal, H/Glc, H																												
	Glc+2-DG, H/Glc, H																												
In vivo: TILs day 30/14	MAA TILs, day 30/14																												
	E7 TILs, day 30/14																												
In vivo: Spl day 90/14	MAA spl, day 90/14																												
	E7 spl, day 90/14																												

Similar to in vitro changes

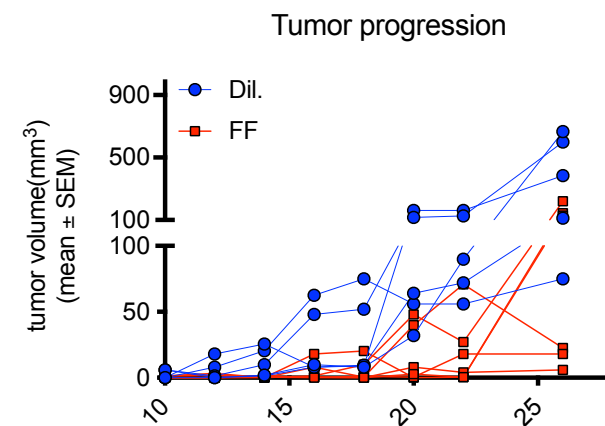
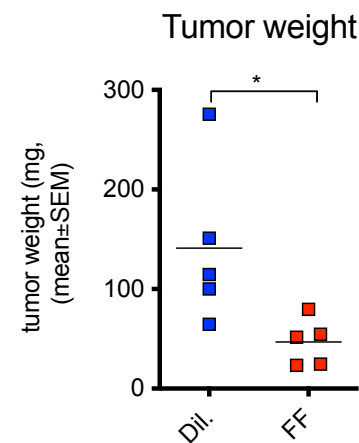
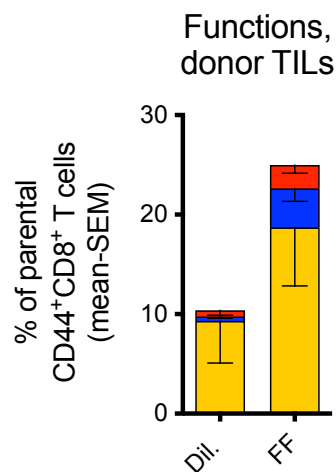
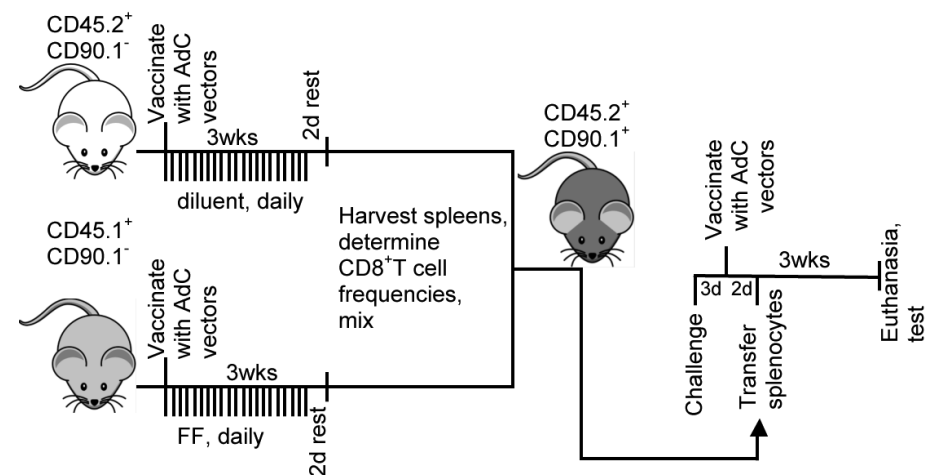
Different from in vitro changes

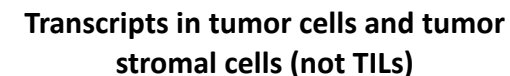
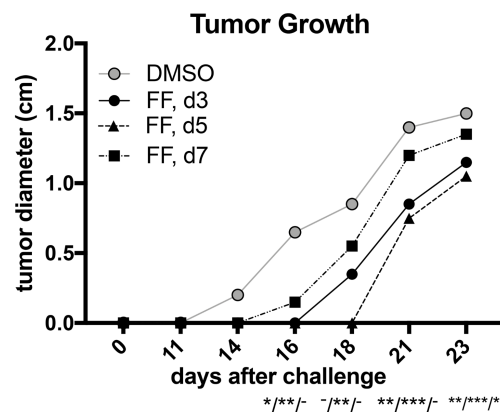
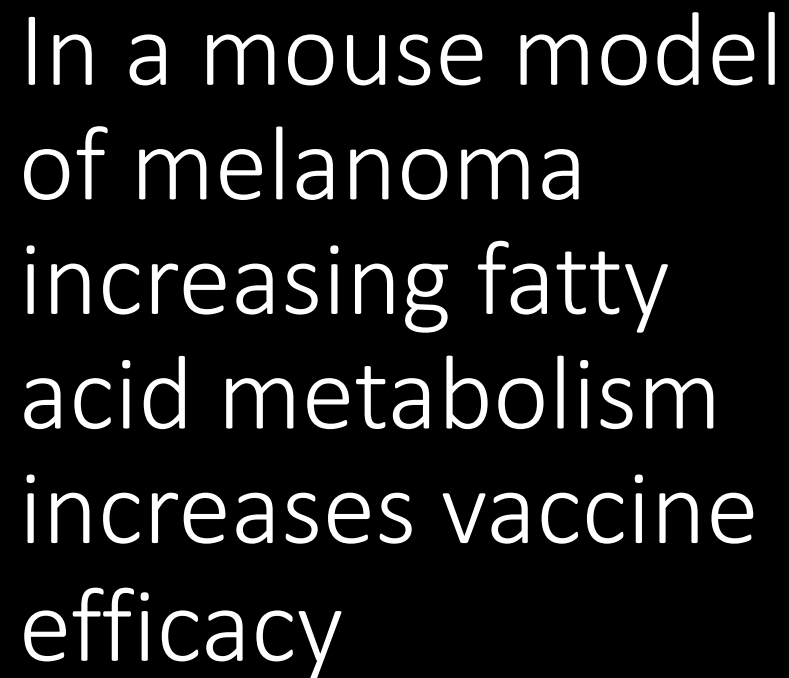
Dependent on culture condition



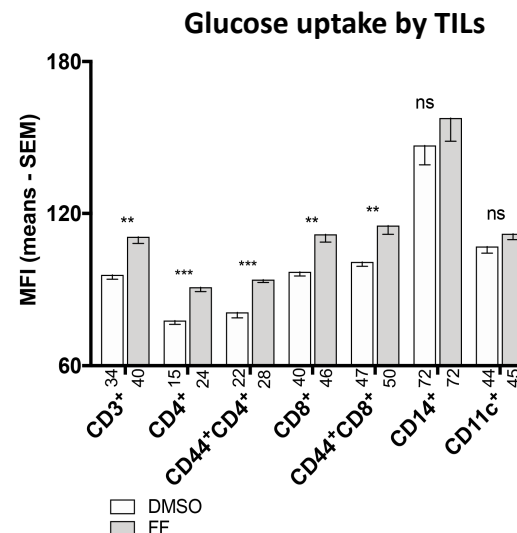
In a mouse melanoma model drug-induced increases in fatty acid metabolism increases the efficacy of adoptively transferred melanoma-specific T cells

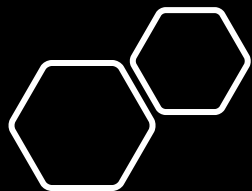
FF-fenofibrate,
a PPAR α agonist



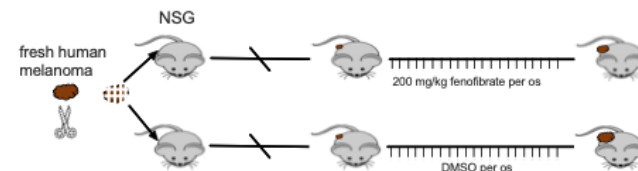
[illegible]

10
-10 o - outliers

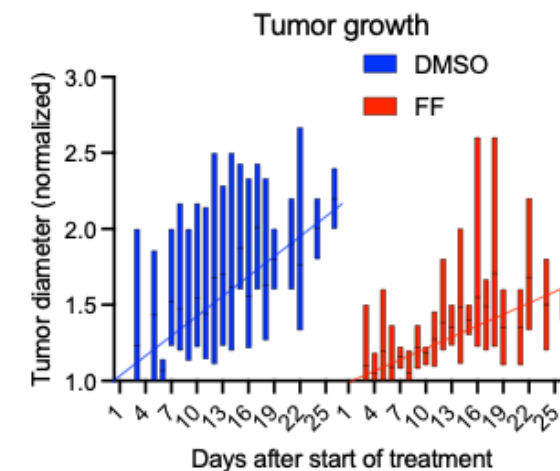




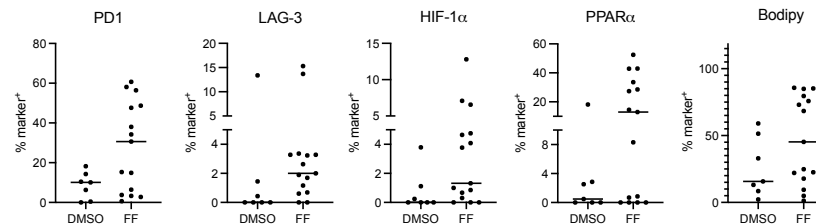
NSG model with fresh human melanoma fragments



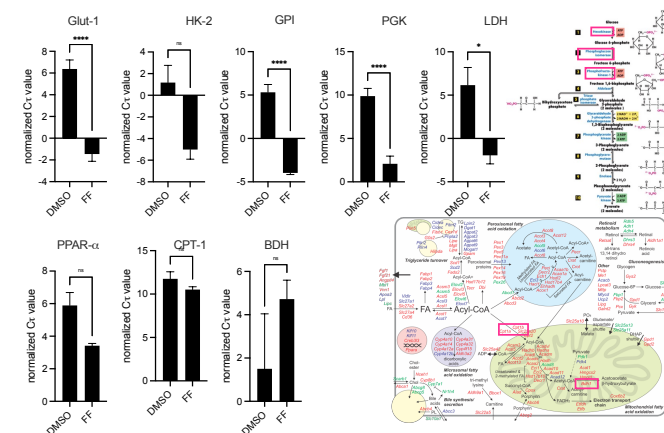
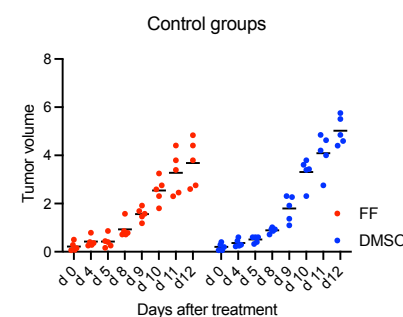
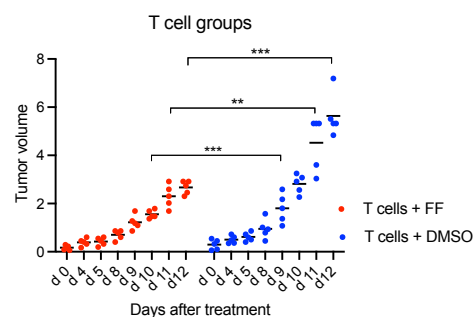
2 recurrent melanomas,
1 metastatic melanoma,
1 primary melanoma



Human CD8⁺ PBMCs

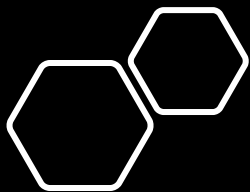


Metastatic Melanoma



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



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