



Metabolic Adaptations Establish Immunotherapy Resistance in Melanoma

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Department of Immunology

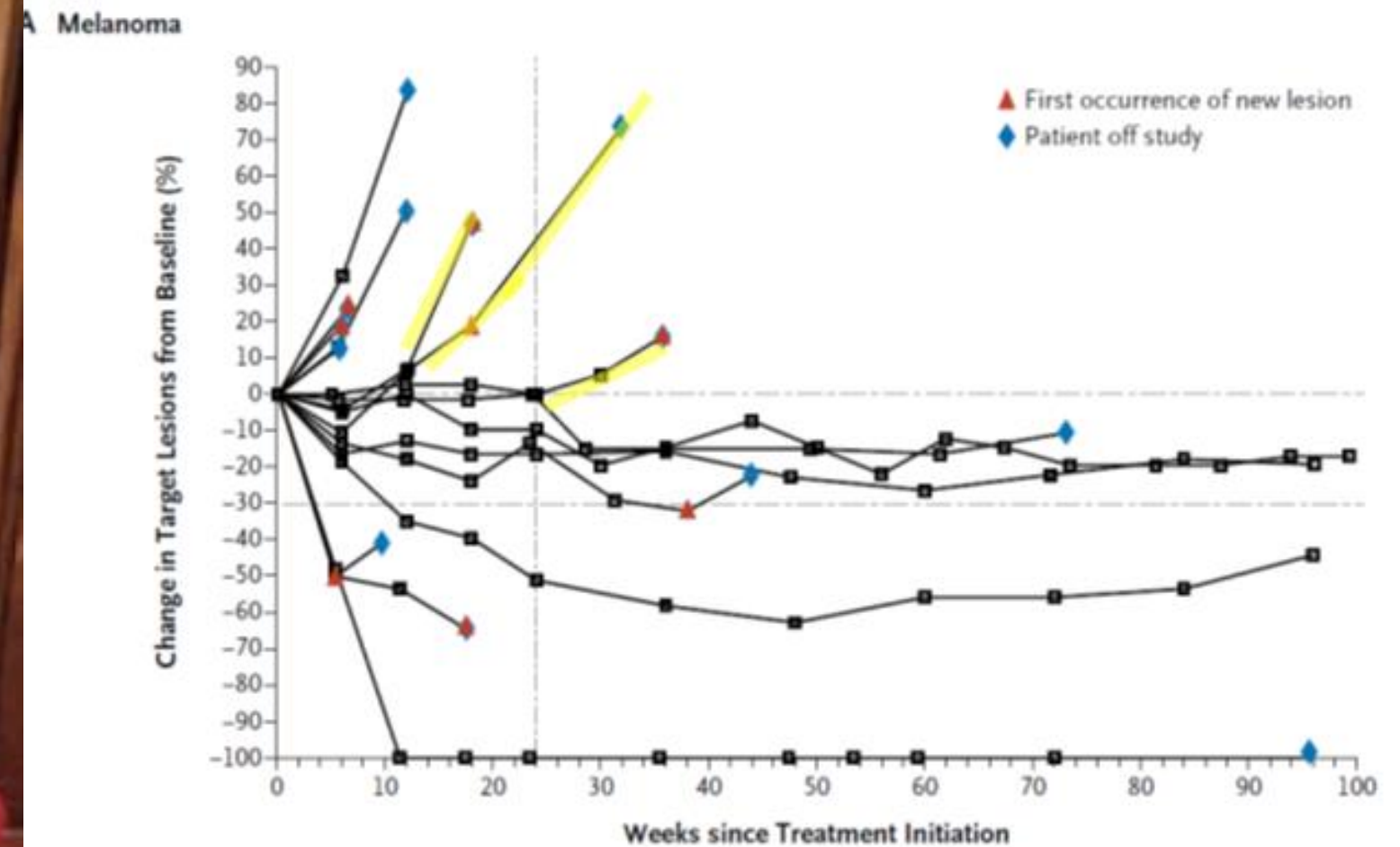
Disclosures

**I have no financial relationships to
disclose.**

Tumor Immunotherapy

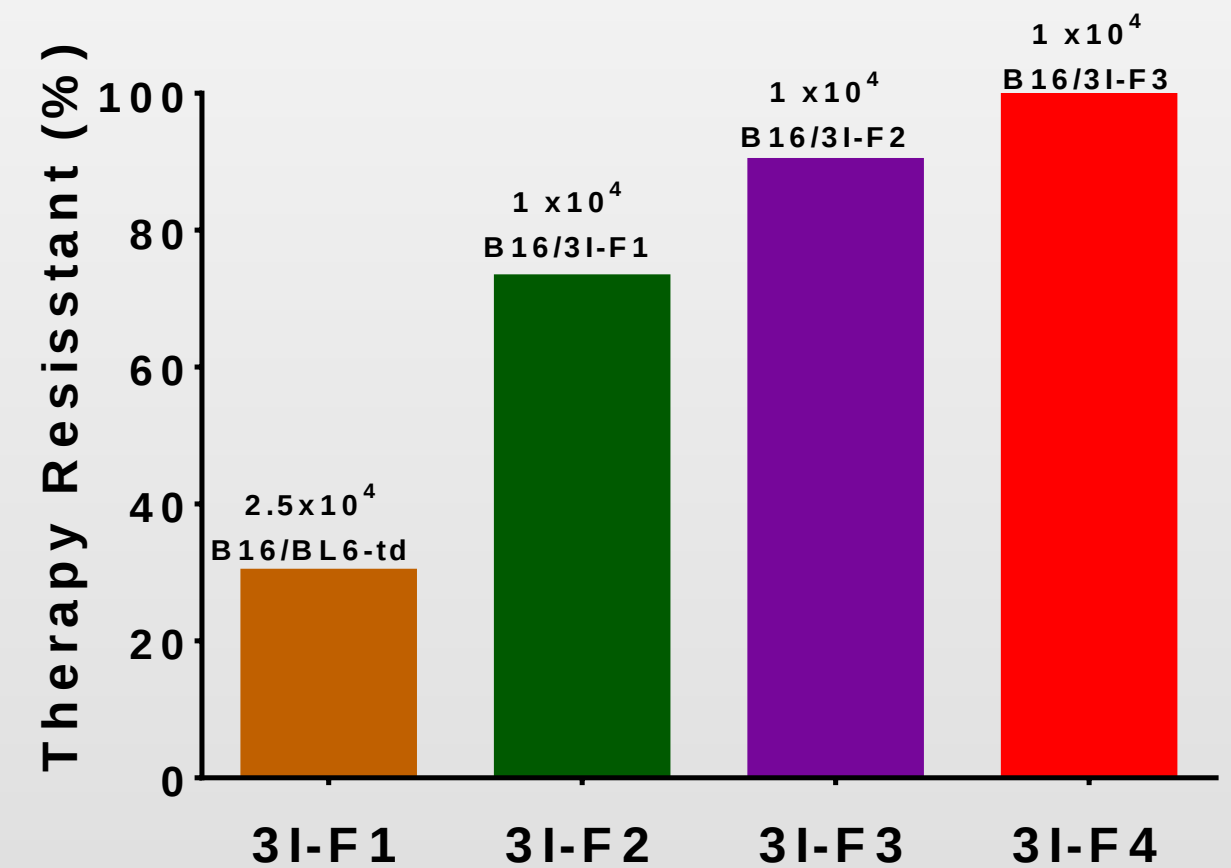
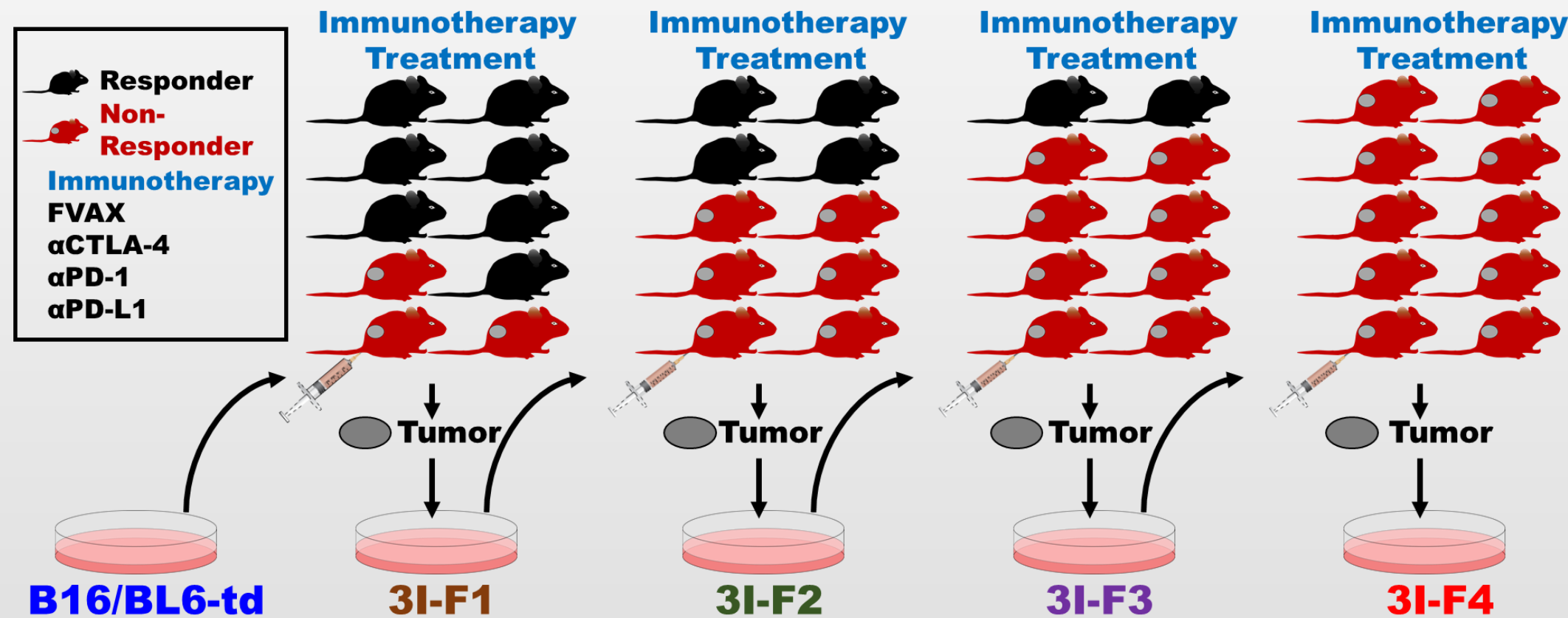


Acquired Resistance to Immunotherapy



NEJM 366;26 June 28, 2012

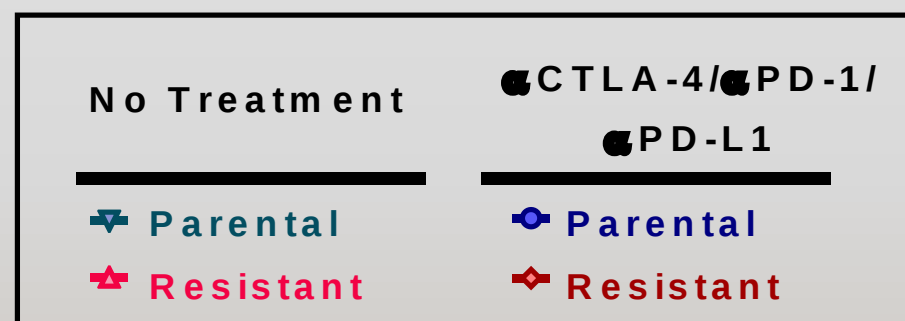
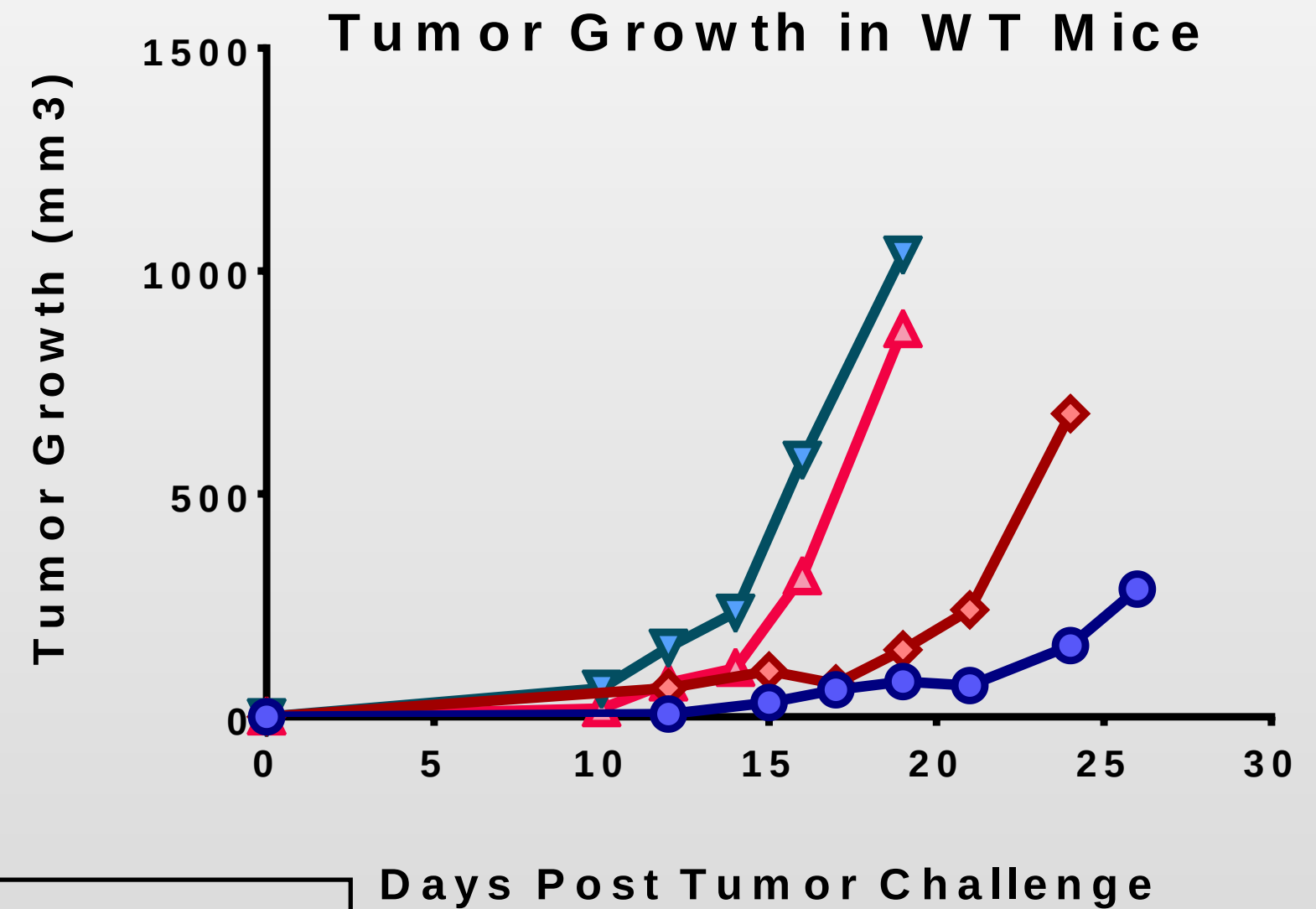
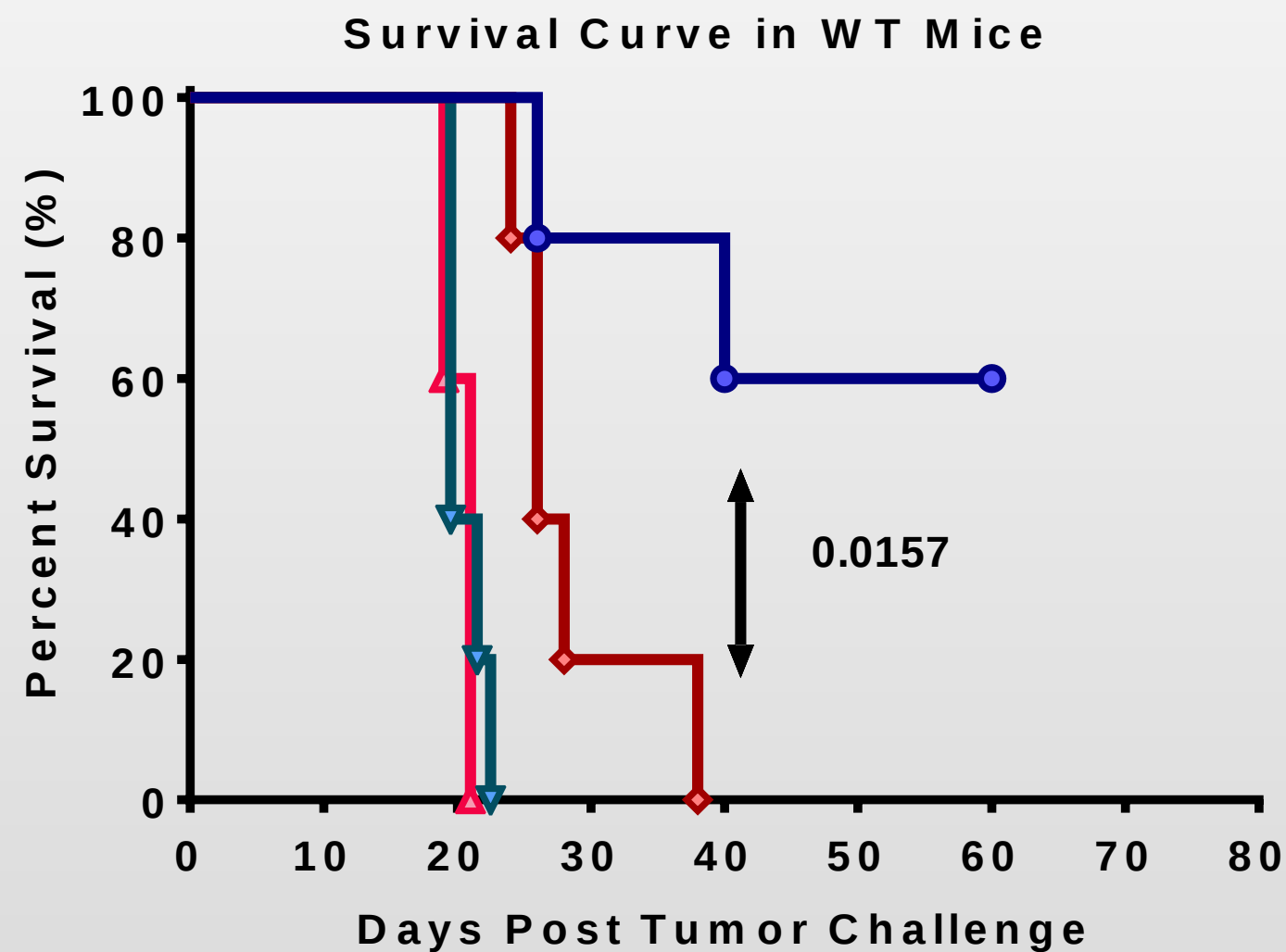
Evolving Immunotherapy Resistant Murine Melanoma



- Immunoediting theory (Robert D. Schreiber)
- B16/F10 Metastatic Tumors (Dr. Fidler)
- Curran et al., PNAS 2010

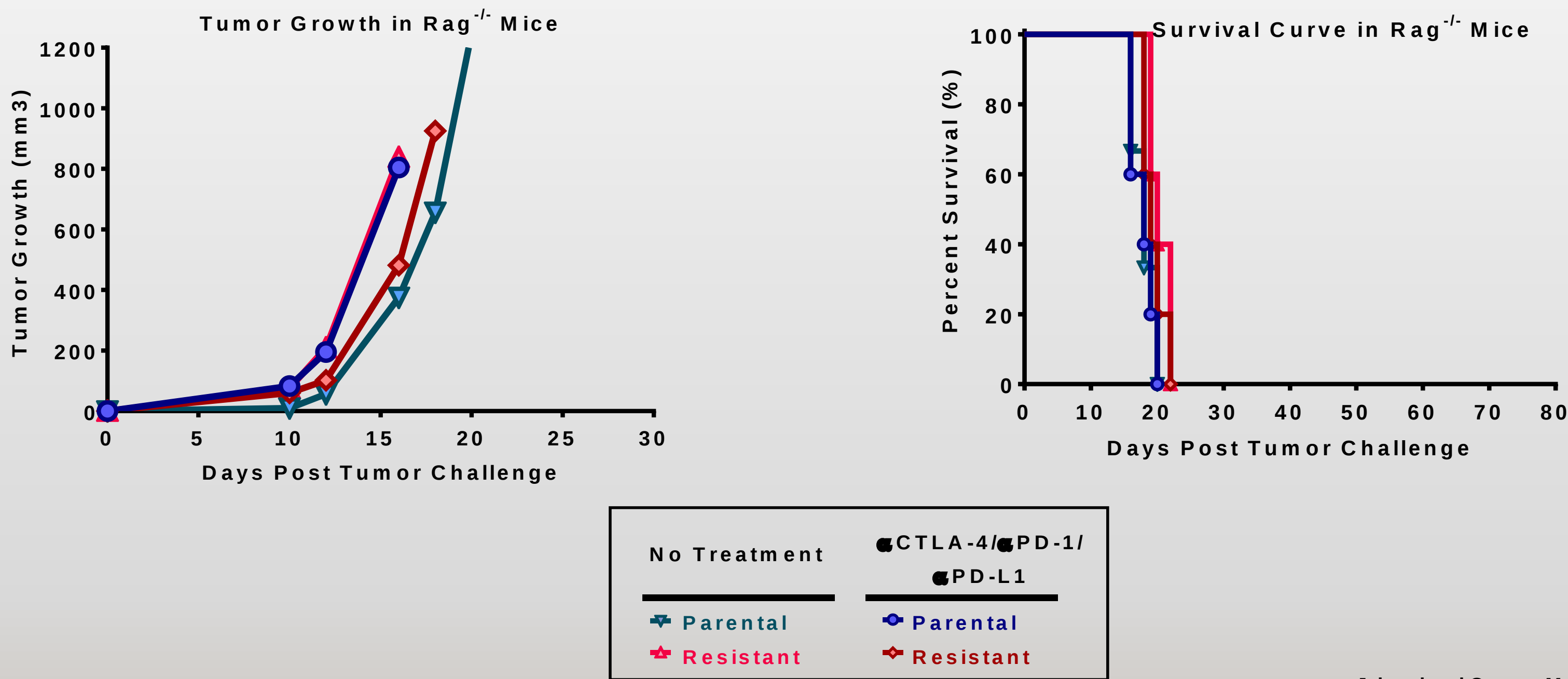
Immunotherapy Resistant Murine Melanoma

In vivo tumor growth and survival of resistant cell line in WT Mice

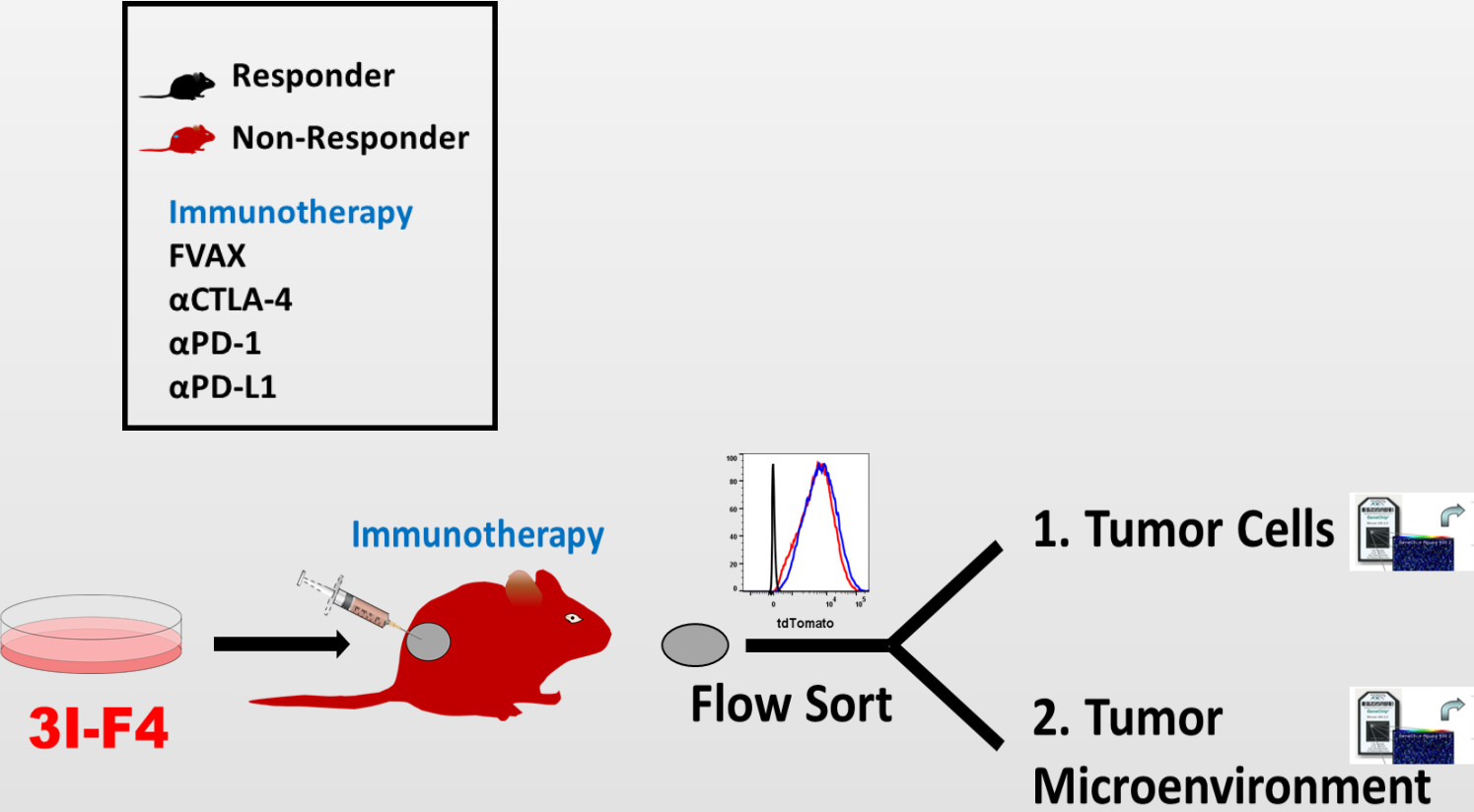


Resistance in 3I-F4 Cells is Immune Driven

In vivo tumor growth and survival of resistant cell line in Rag^{-/-} Mice

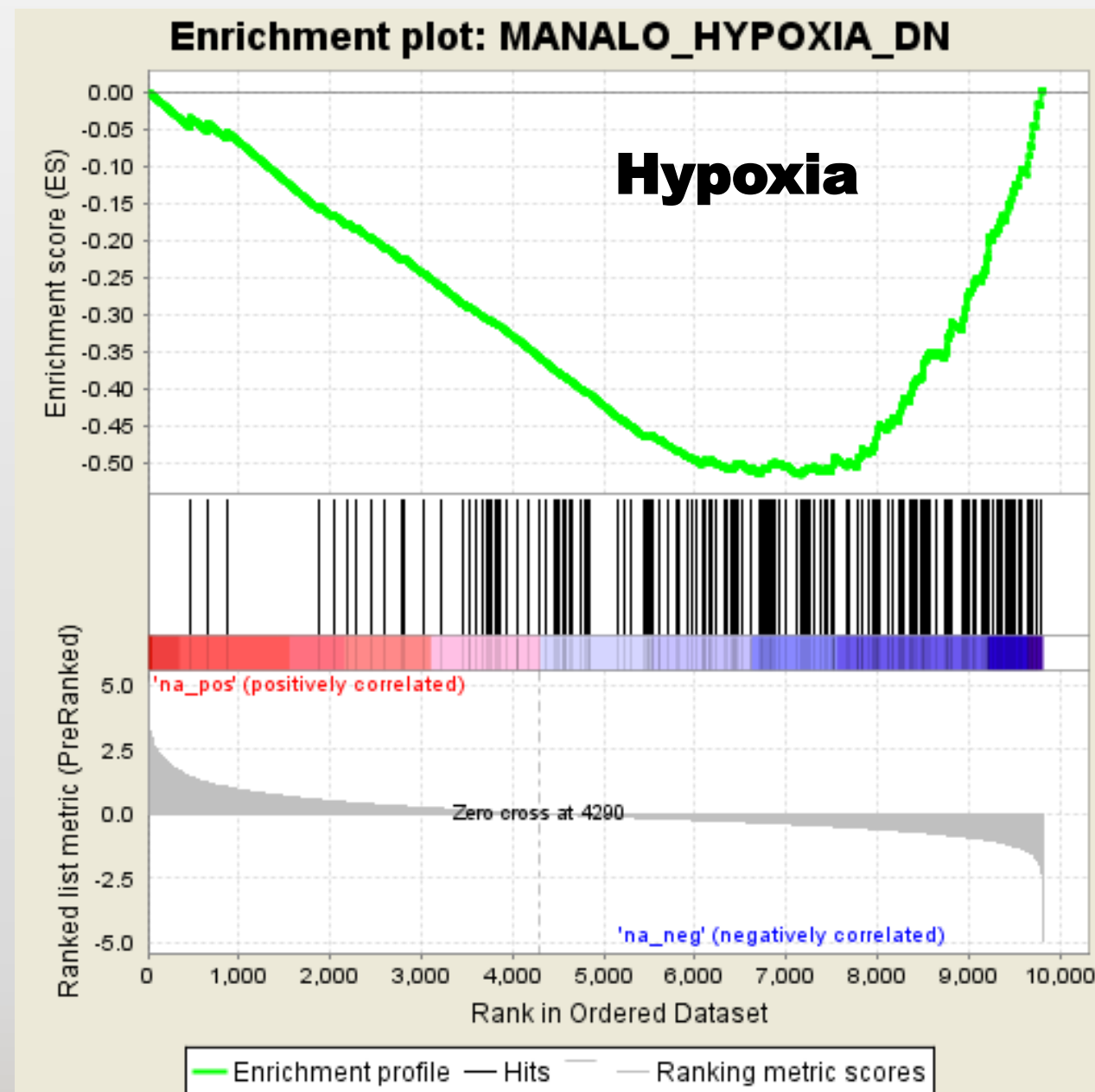


Gene Expression Analysis of Resistant Tumor and Microenvironment

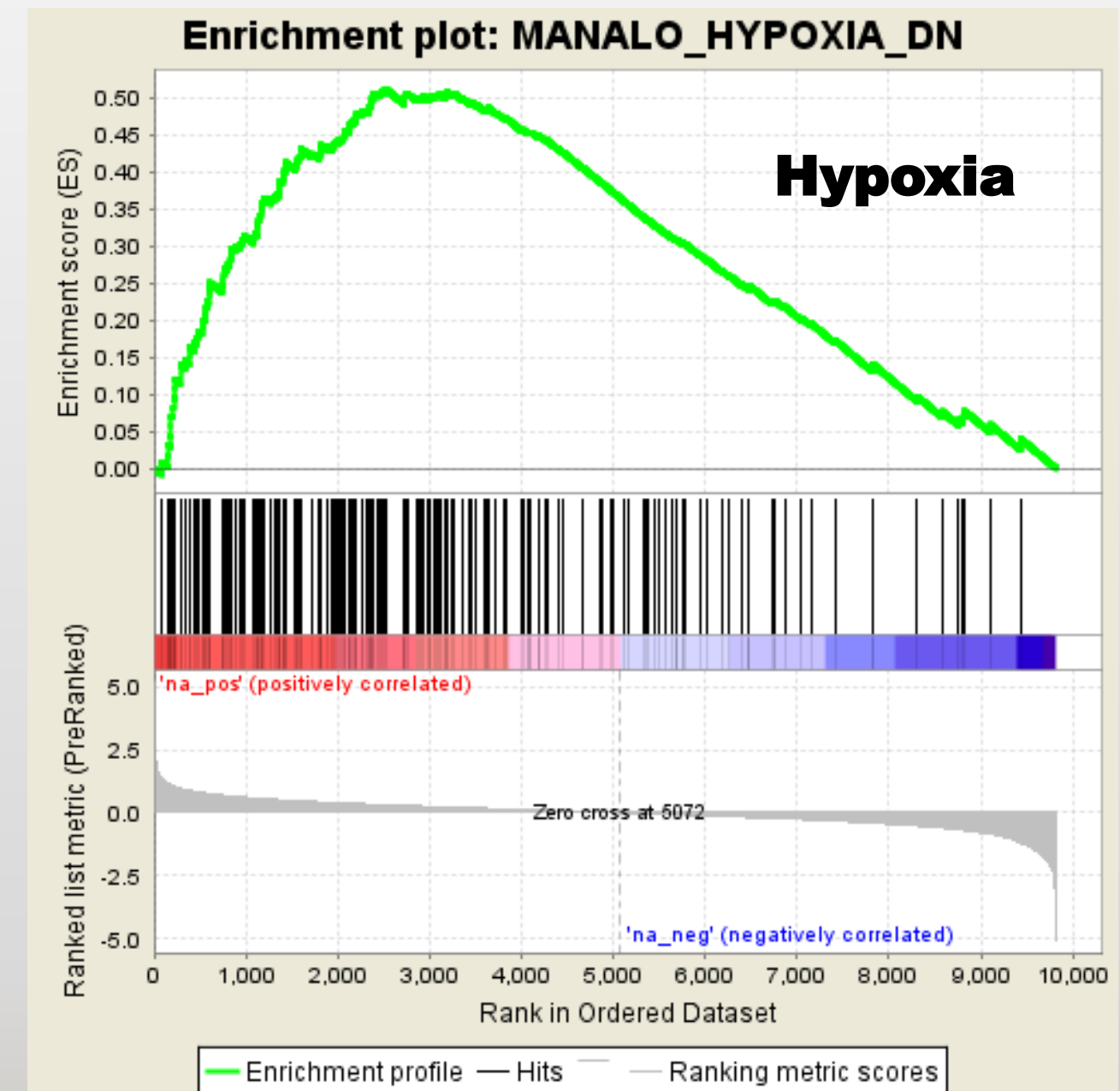


Metabolic Adaptation of Resistant Tumor and Microenvironment : GSEA

Tumor Microenvironment

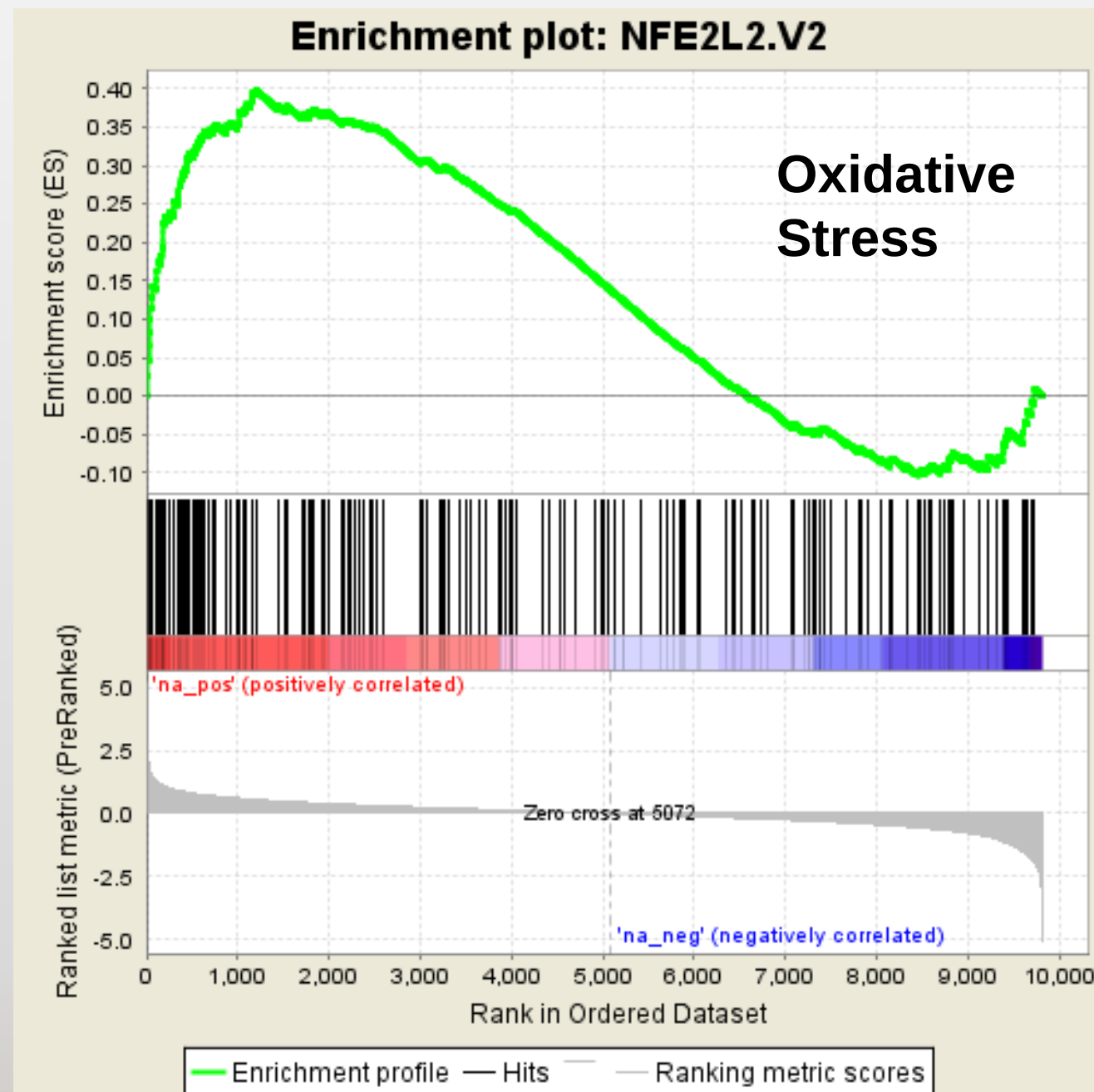


Tumor Cells

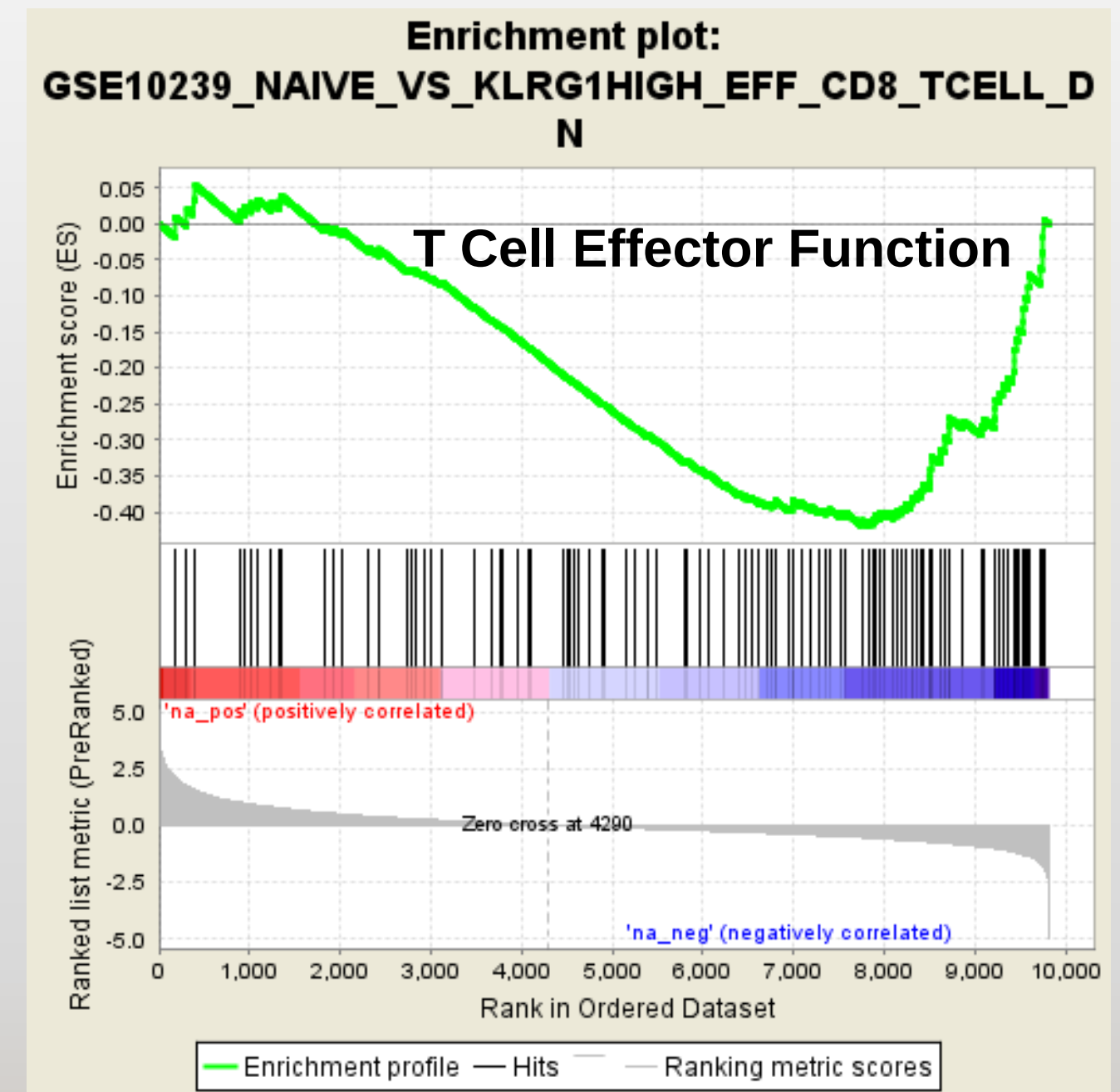


Metabolic Adaptation of Resistant Tumor and Microenvironment : GSEA

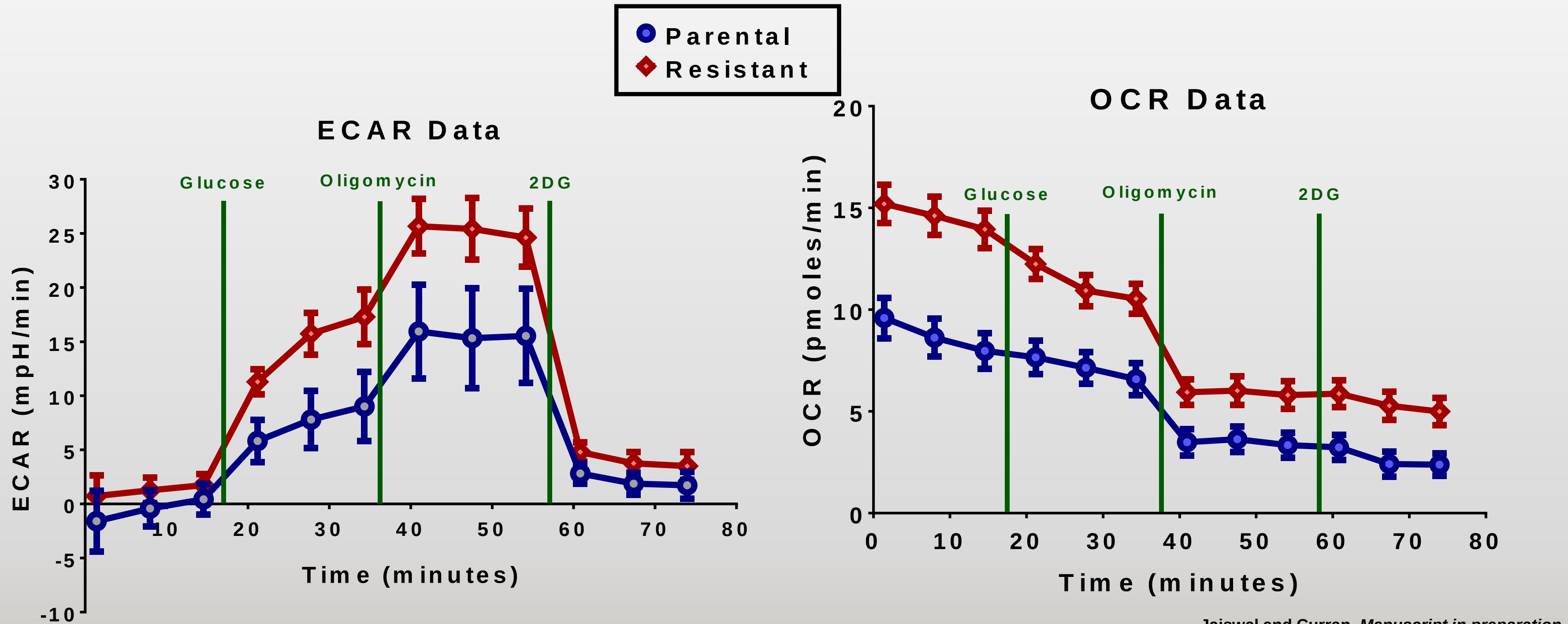
Tumor Cells



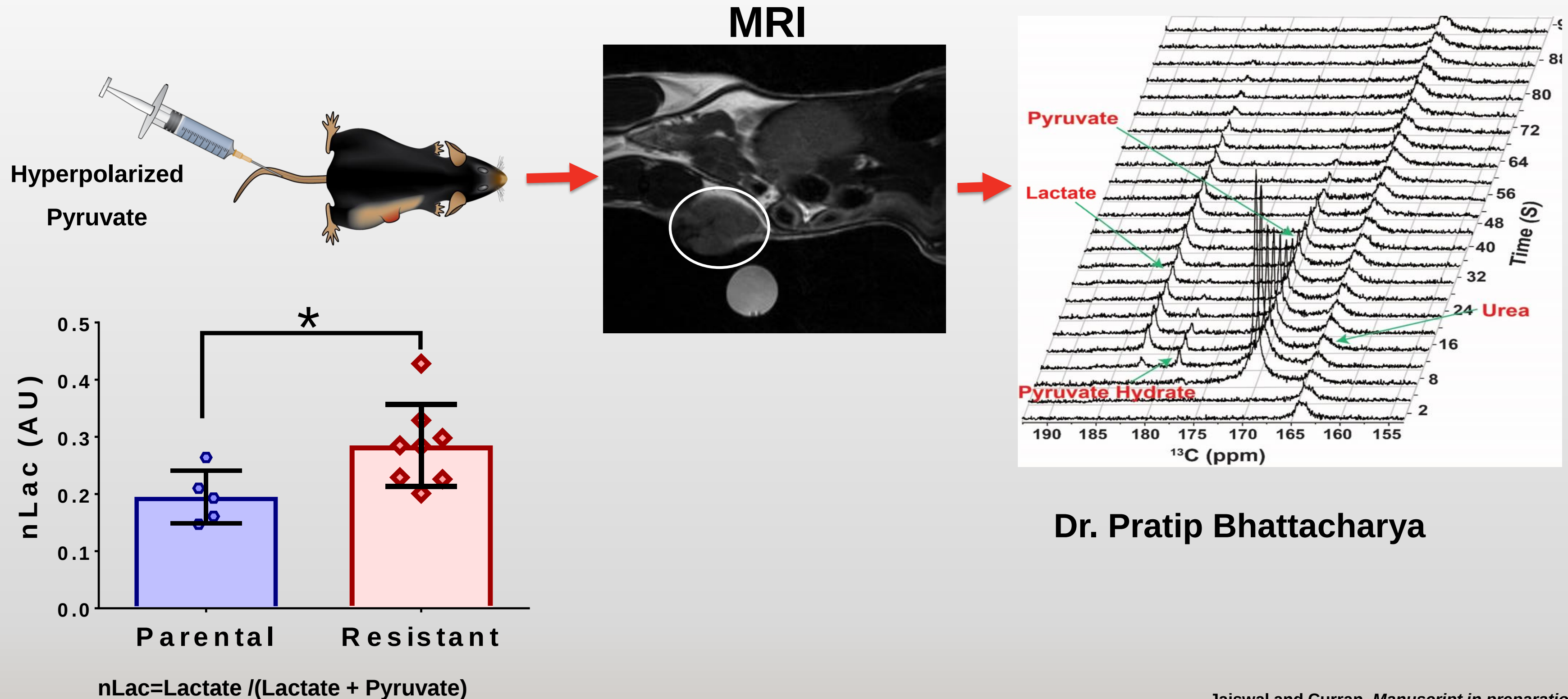
Tumor Microenvironment



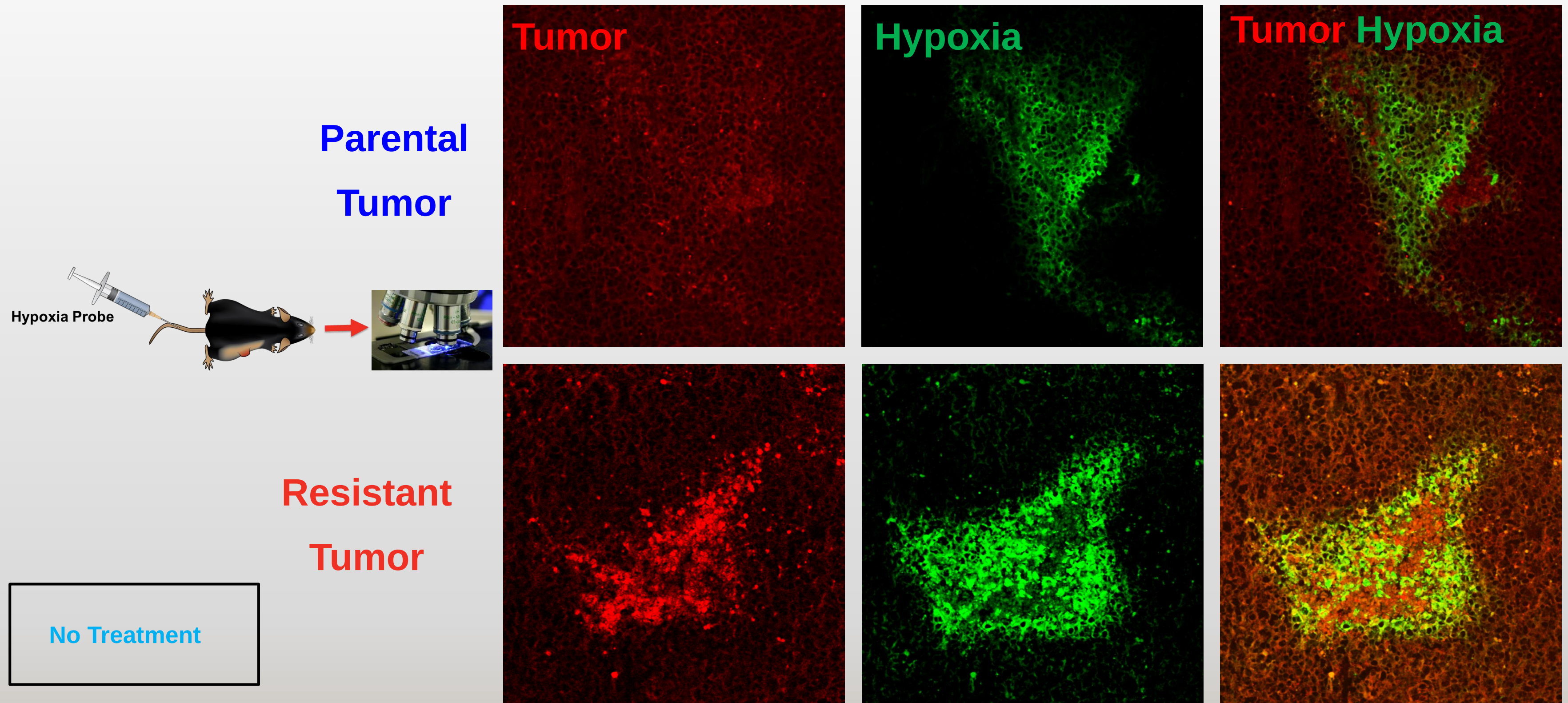
Resistant Tumor Cell Line Increased Glycolytic and Oxphos: Seahorse



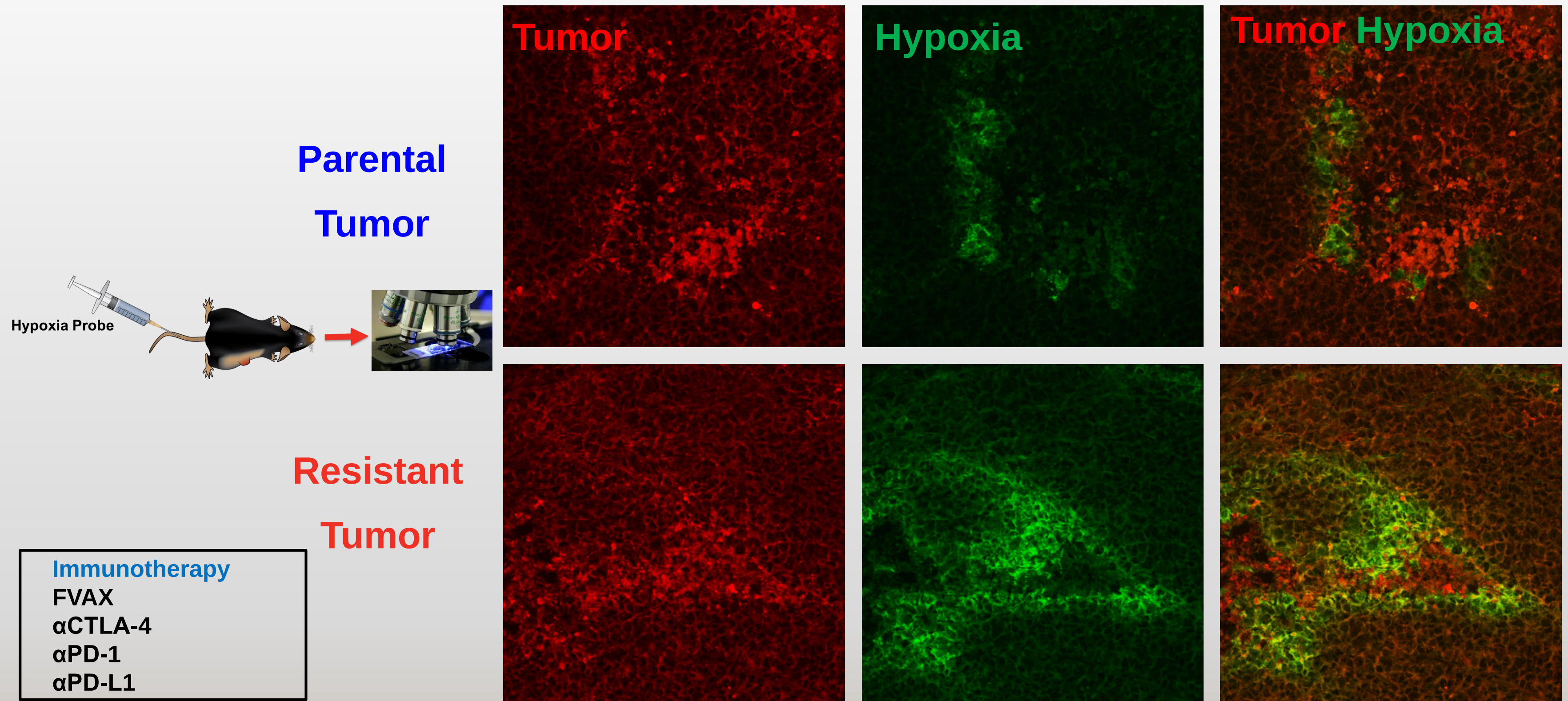
Resistant Tumor Stood High on Glycolysis: Noninvasive MRI Imaging in Live Mice



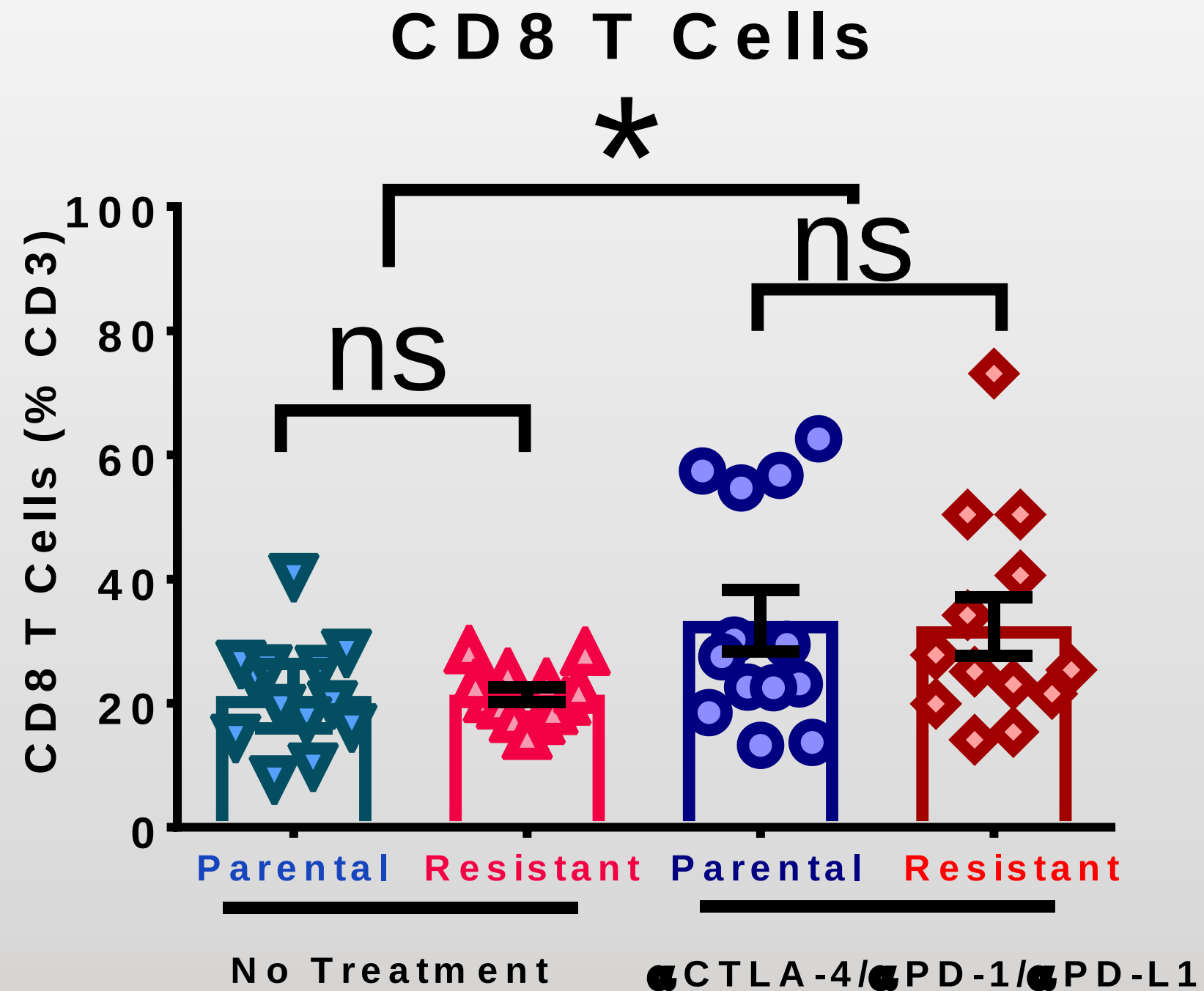
Resistant Tumor Cells Adapted to Survive in Hypoxic Tumor: No Treatment



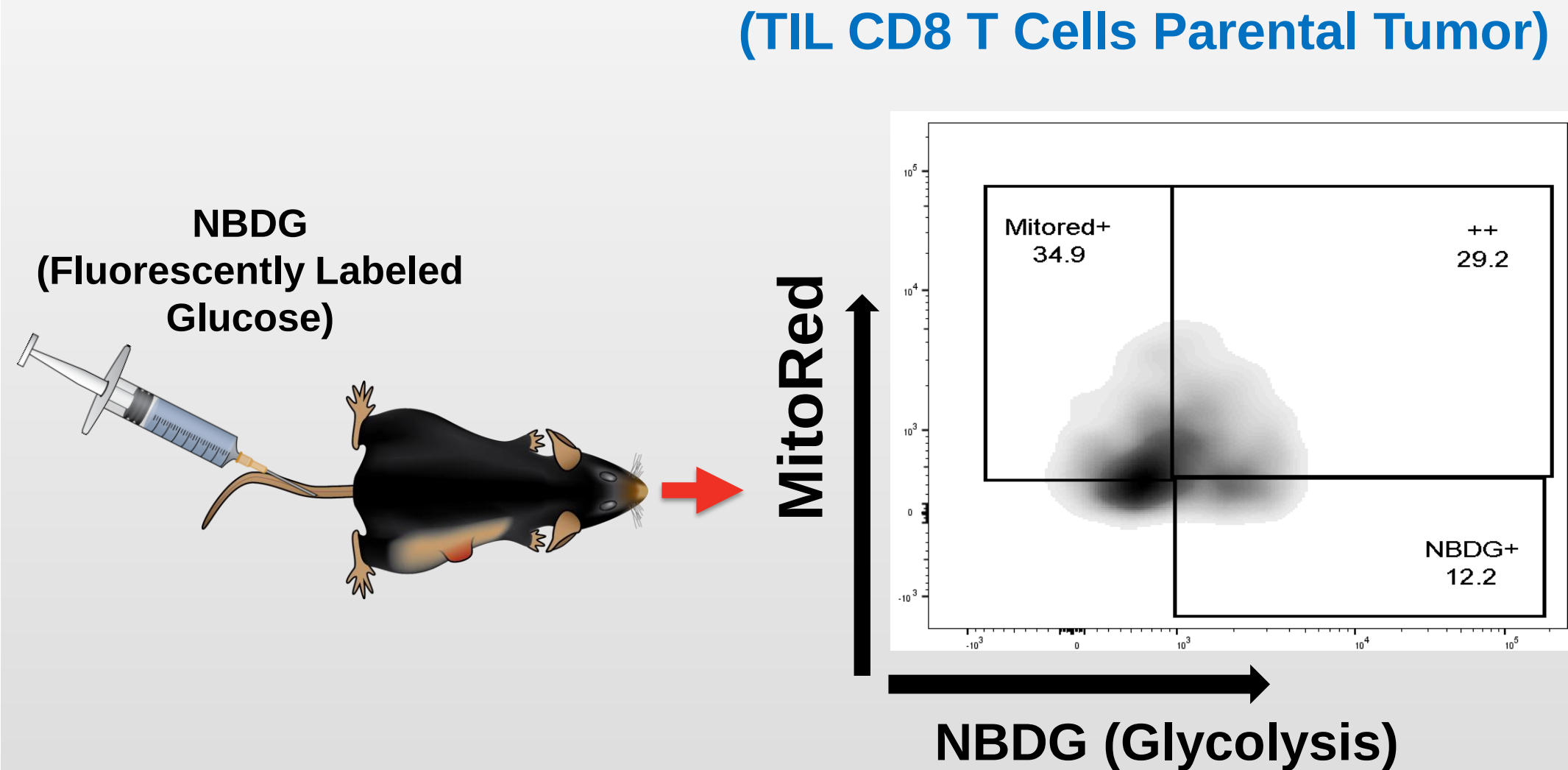
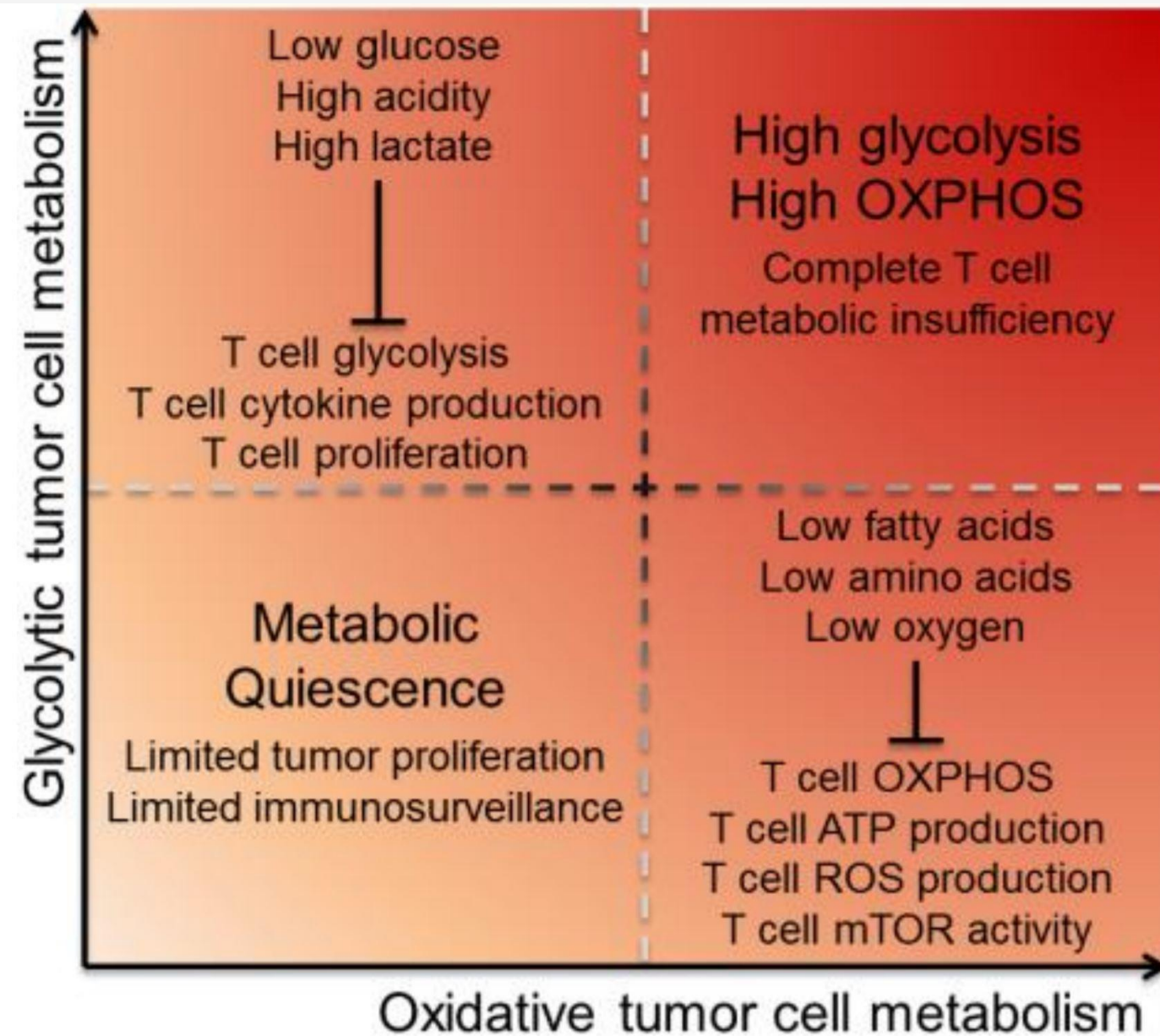
Resistant Tumor Cells Adapted to Survive in Hypoxic Tumor: Treatment



CD8 T Cells Infiltration were Unaffected in Resistant Tumor

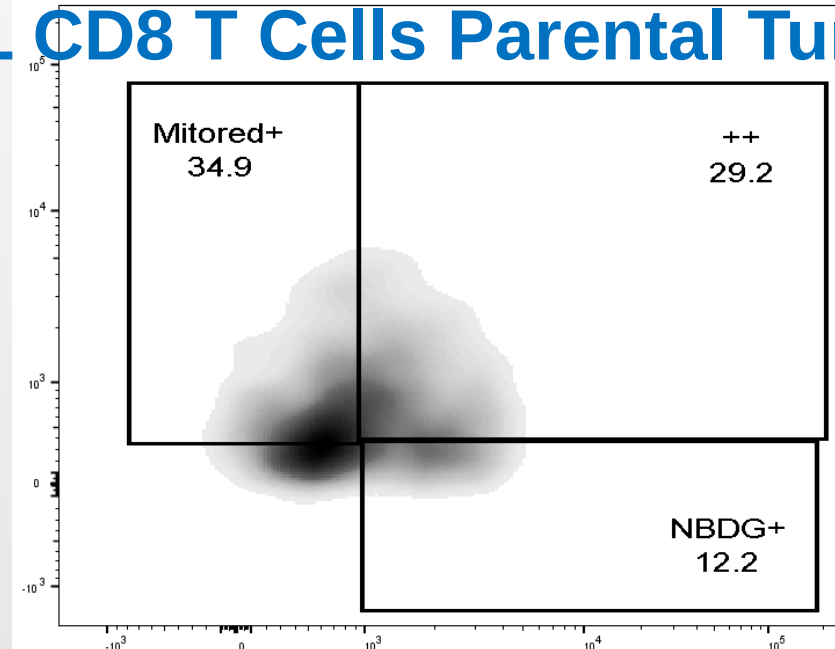


Effect of Metabolic Adaptation of Tumors on Immune Component

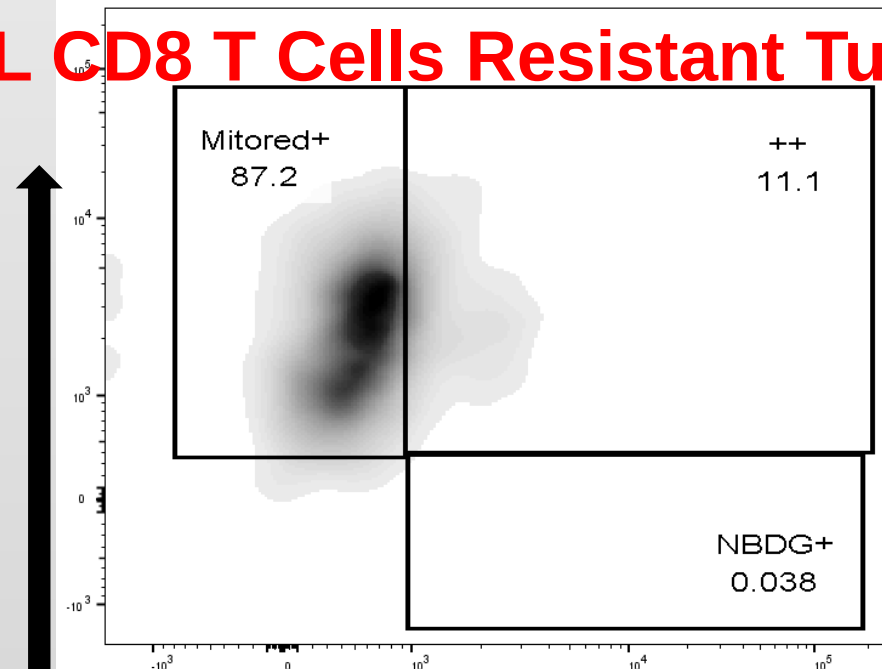


Tumor Infiltrating CD8 T Cells Lost Glycolytic Capacity and Effector Function

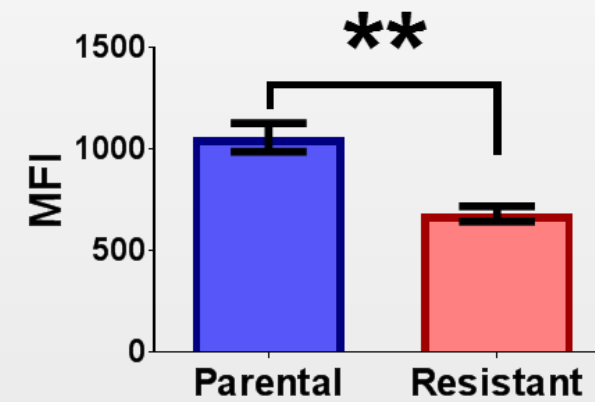
(TIL CD8 T Cells Parental Tumor)



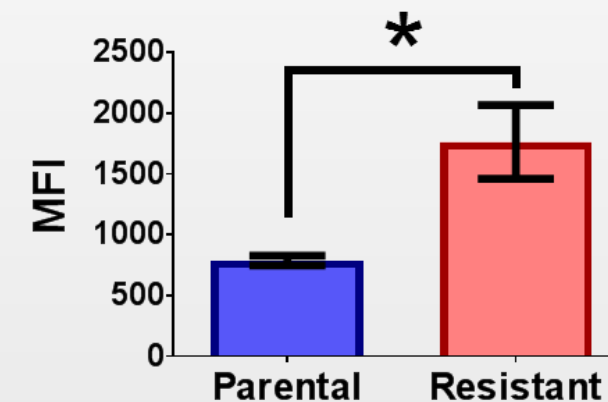
(TIL CD8 T Cells Resistant Tumor)



Glycolysis

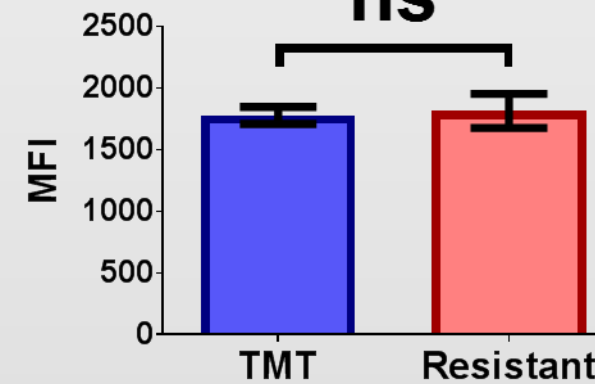


MitoRed

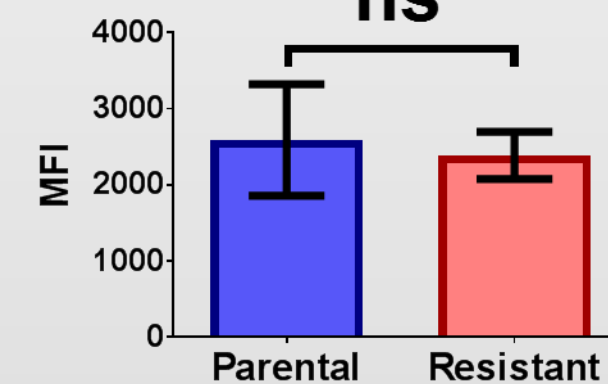


TIL CD8

ns

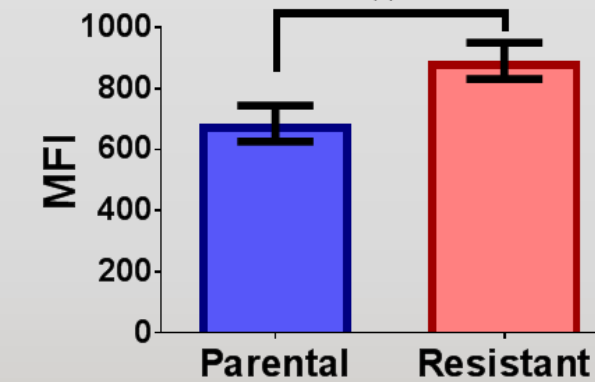


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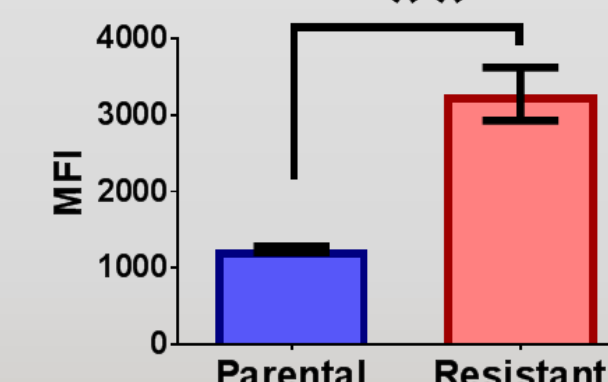


Spleen CD8

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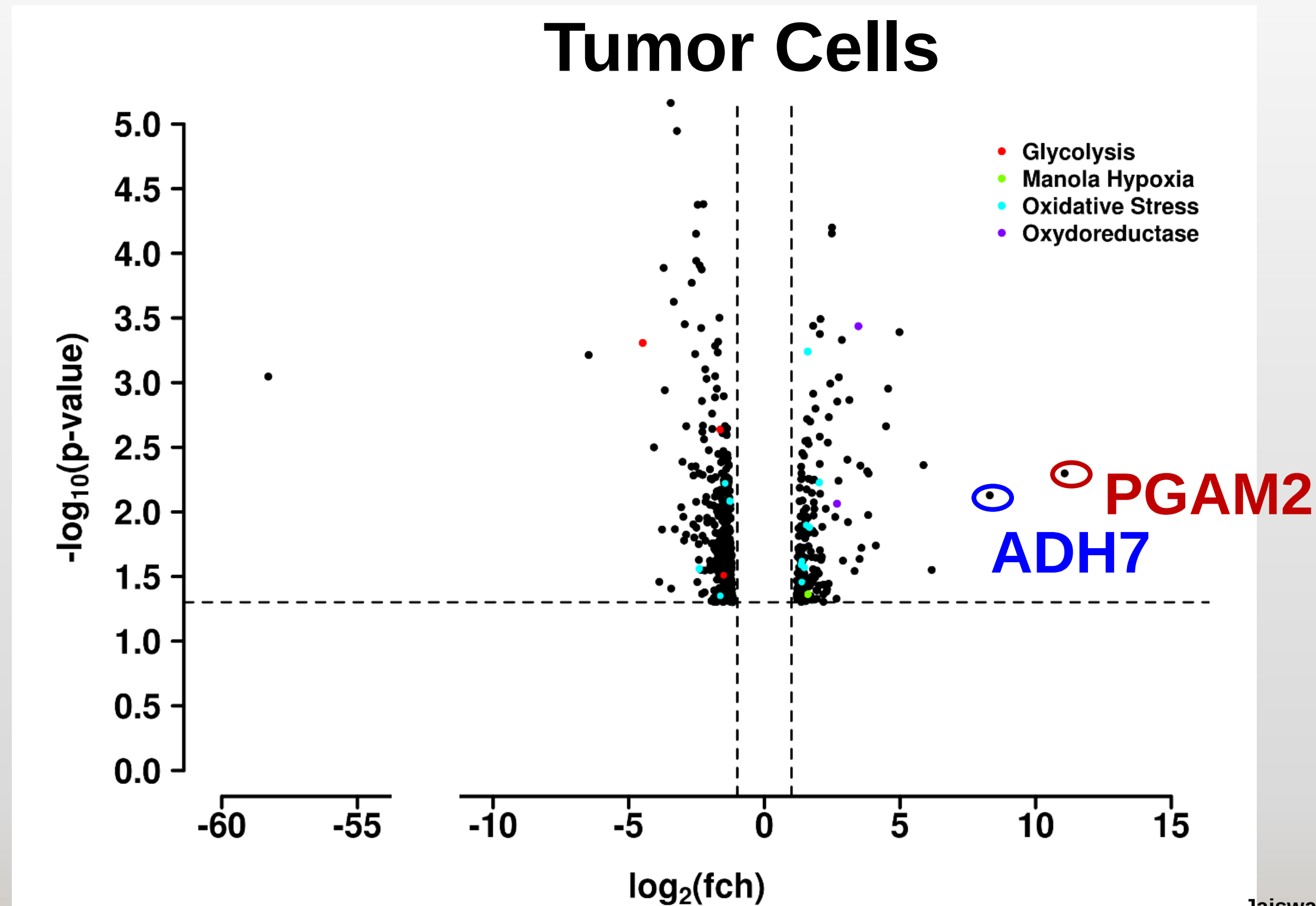


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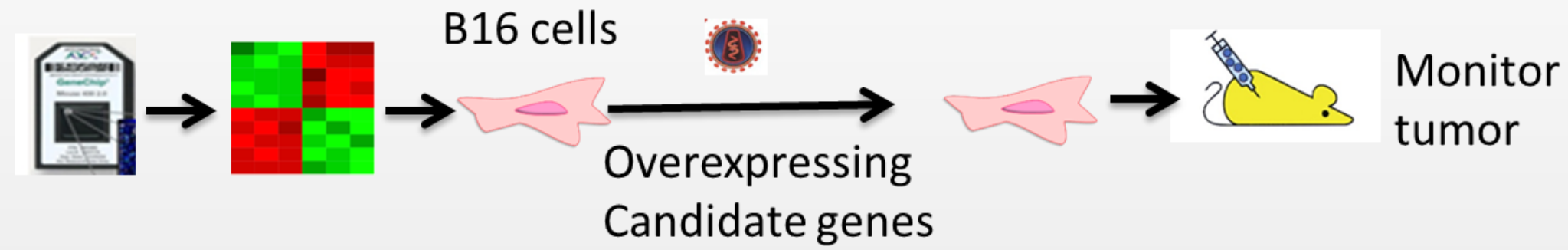


Tumor Cells

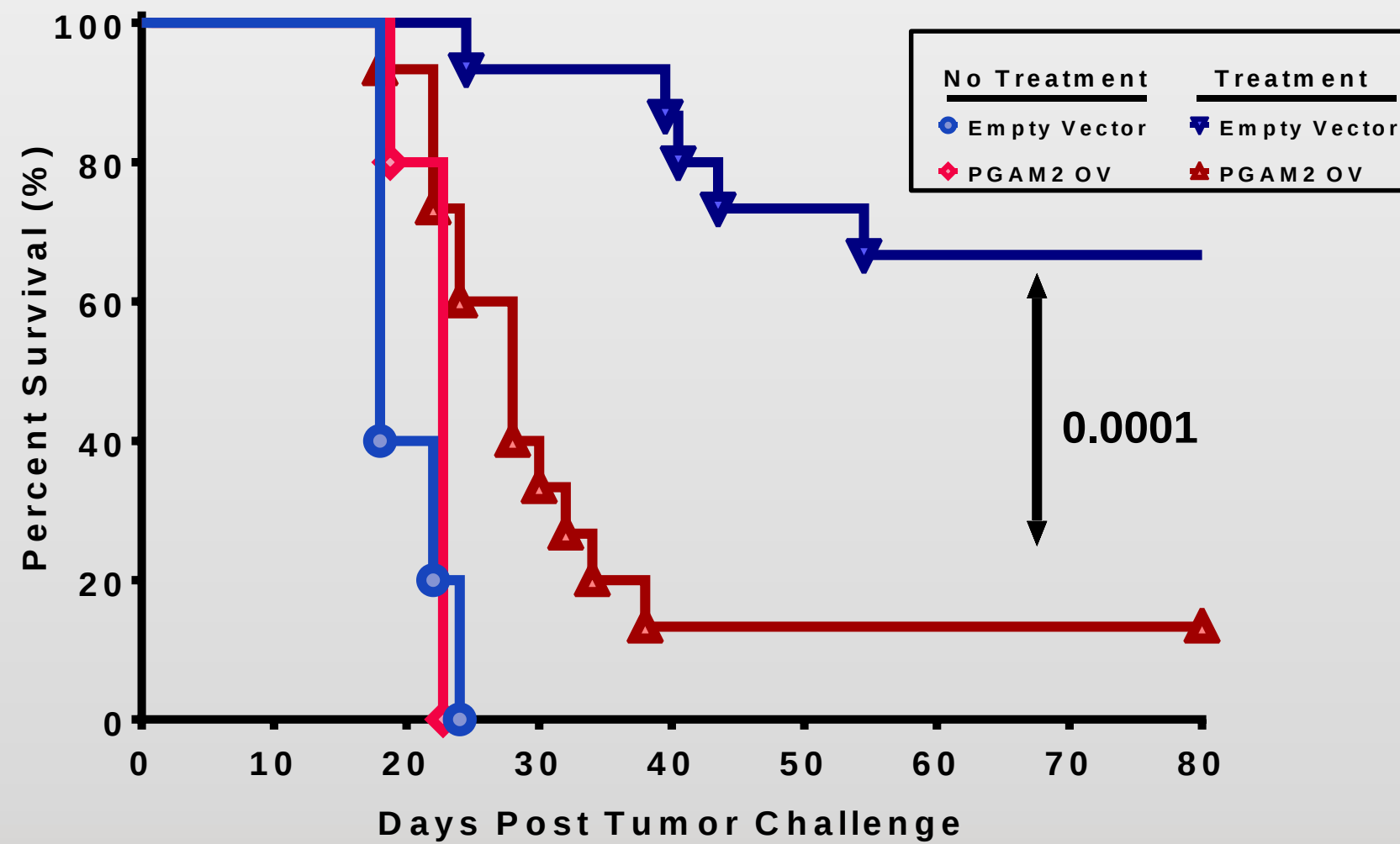
Genetic Signature of Immunotherapy Resistant Melanoma Tumors



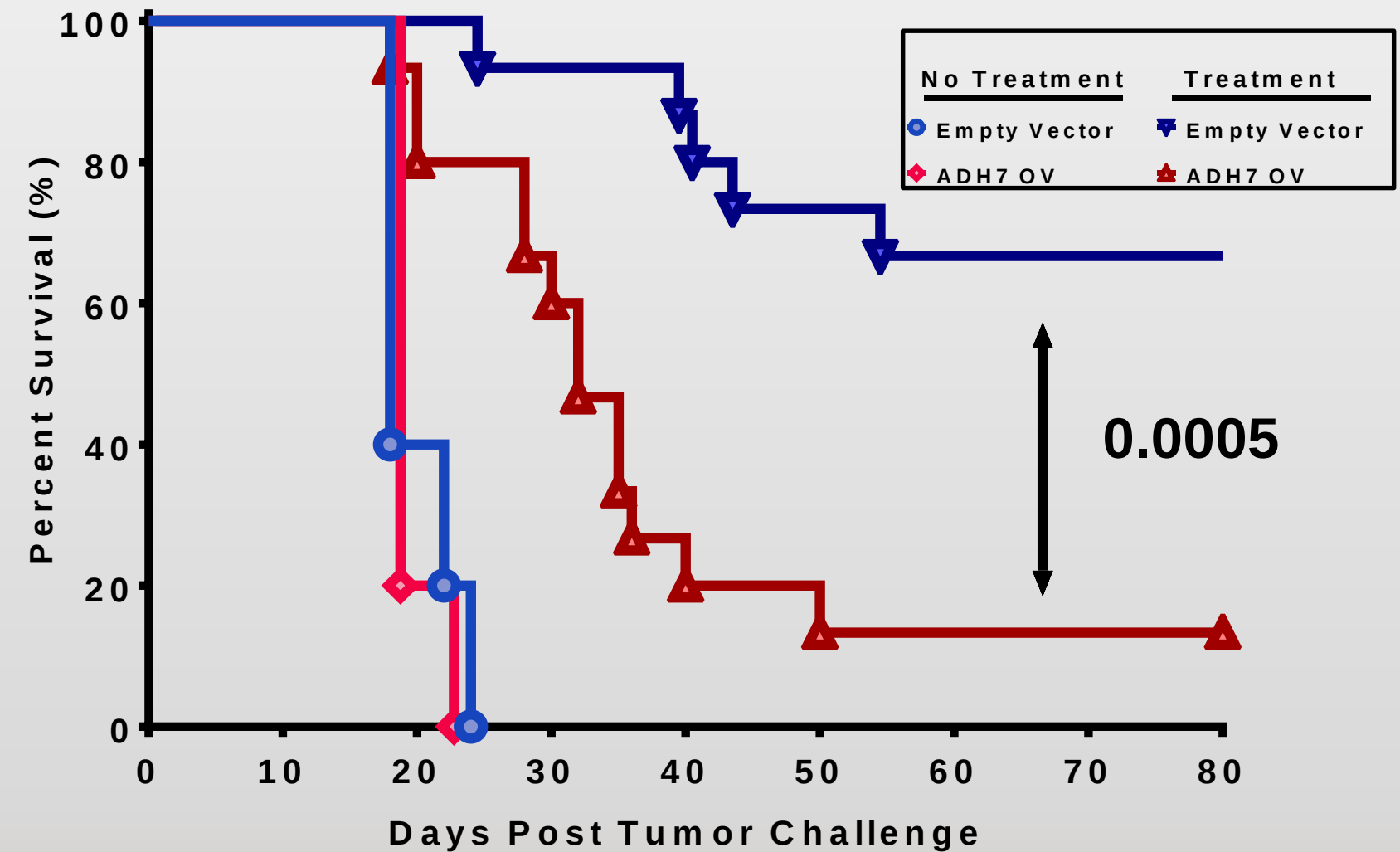
Upregulation of Candidate Genes in Parental Cells Conferred the Immunotherapy Resistance



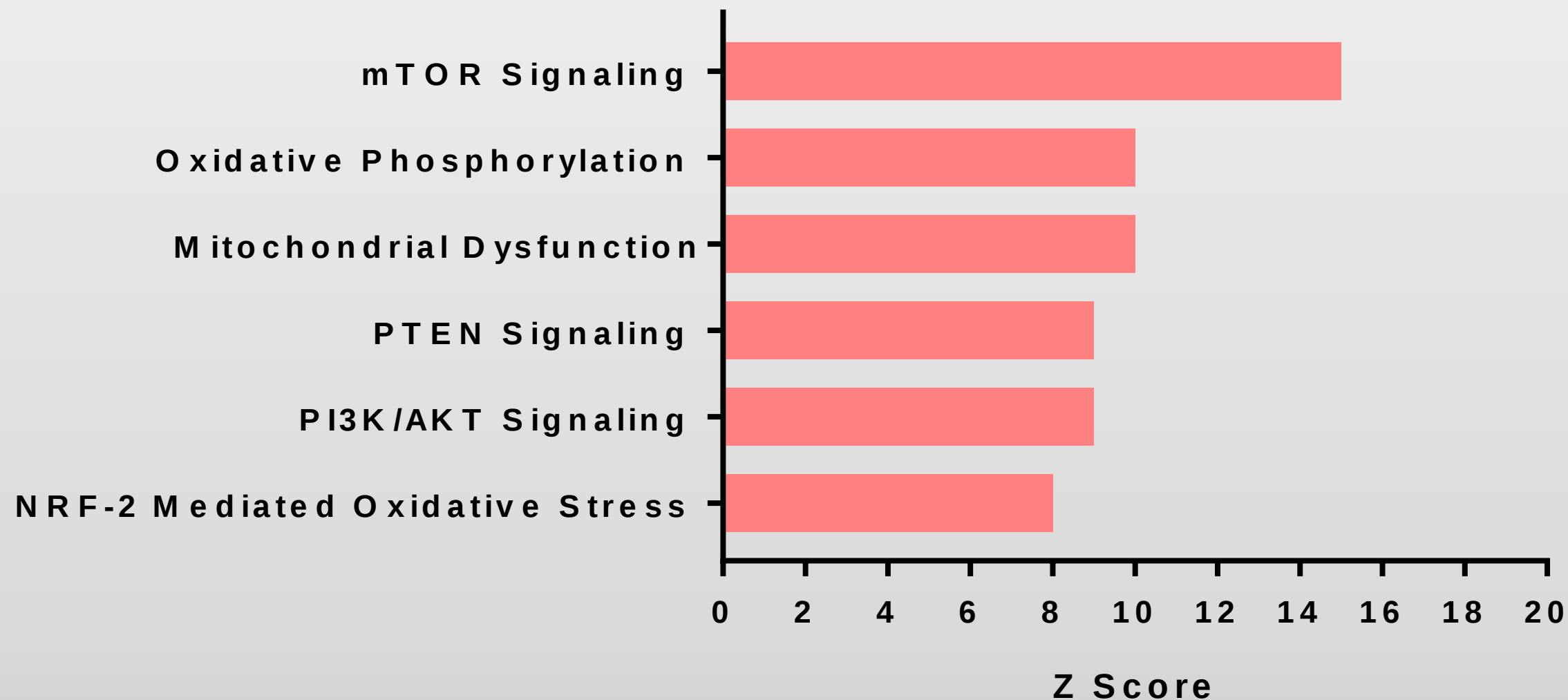
Survival Curve PGAM2 Overexpressed Tumor



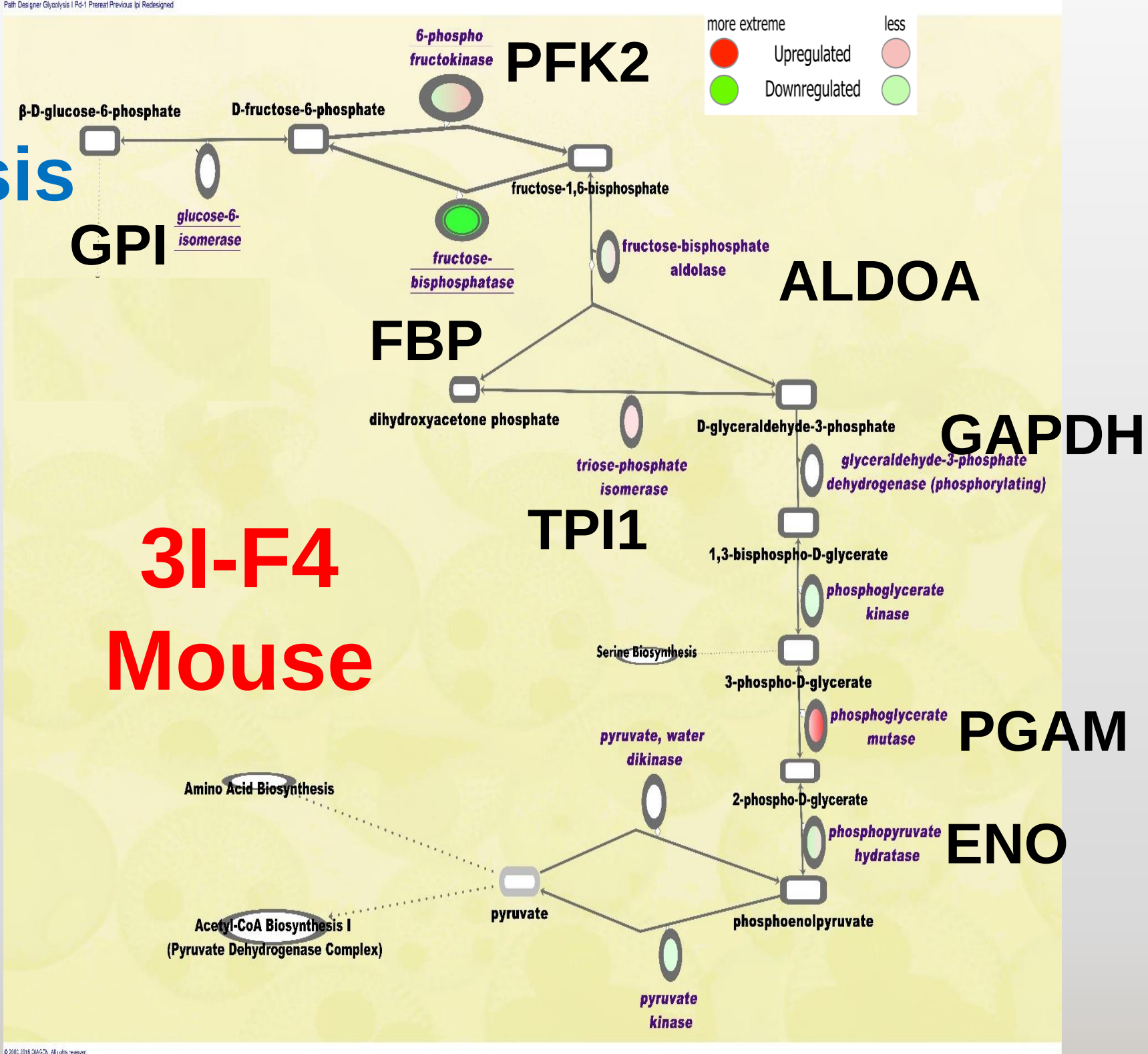
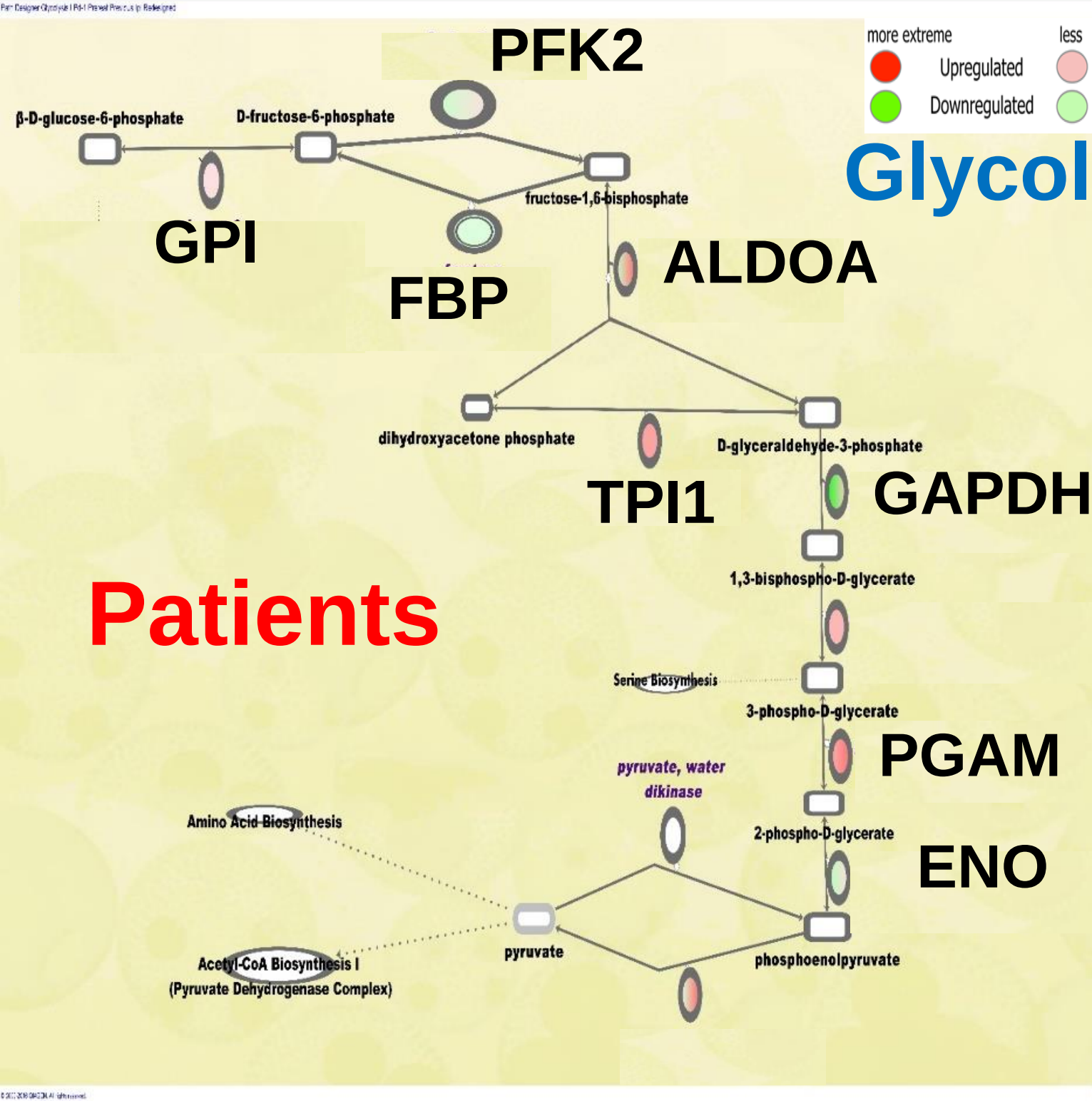
Survival Curve ADH7 Overexpressed Tumor



Patients Resistant to α CTLA-4 and α PD-1 Displayed Similar Metabolic Adaptation: IPA



Patients Resistant to α CTLA-4 and α PD-1 Alter Similar Metabolic Nodes in Glycolysis Pathway



Summary

- Metabolic adaptation drives acquisition of complete immunotherapy resistance in murine melanoma tumors
- Resistant tumors exhibit a hyper-metabolic phenotype with both enhanced glycolysis and oxphos, while nutrient-starved T cells lose glycolytic capacity and associated effector function
- Overexpression of PGAM2 and ADH7 in parental tumors confers resistance to immunotherapy
- Tumors from melanoma patients resistant to both CTLA-4 and PD-1 blockade demonstrate a parallel pattern of metabolic adaptation

Acknowledgements

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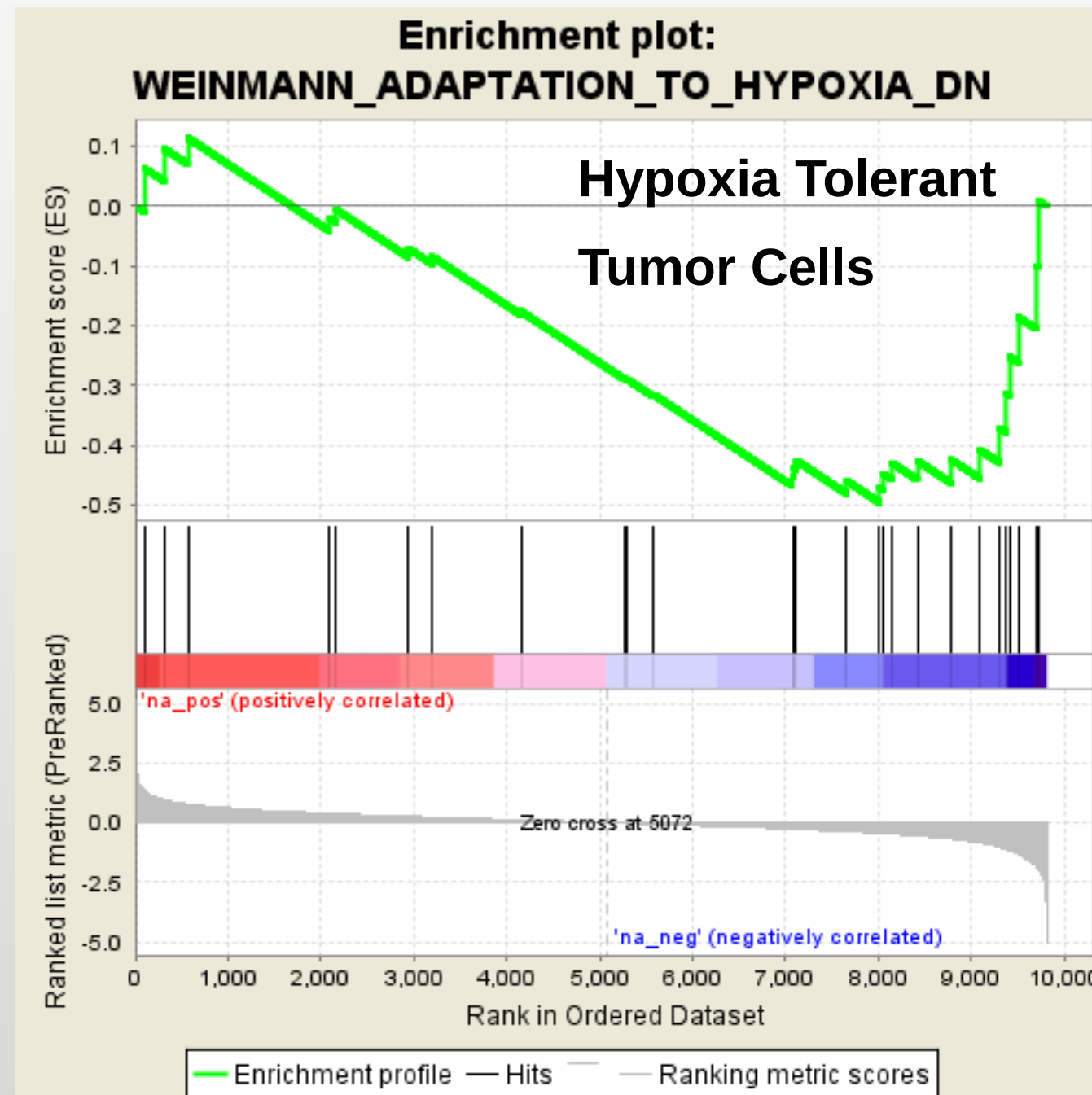
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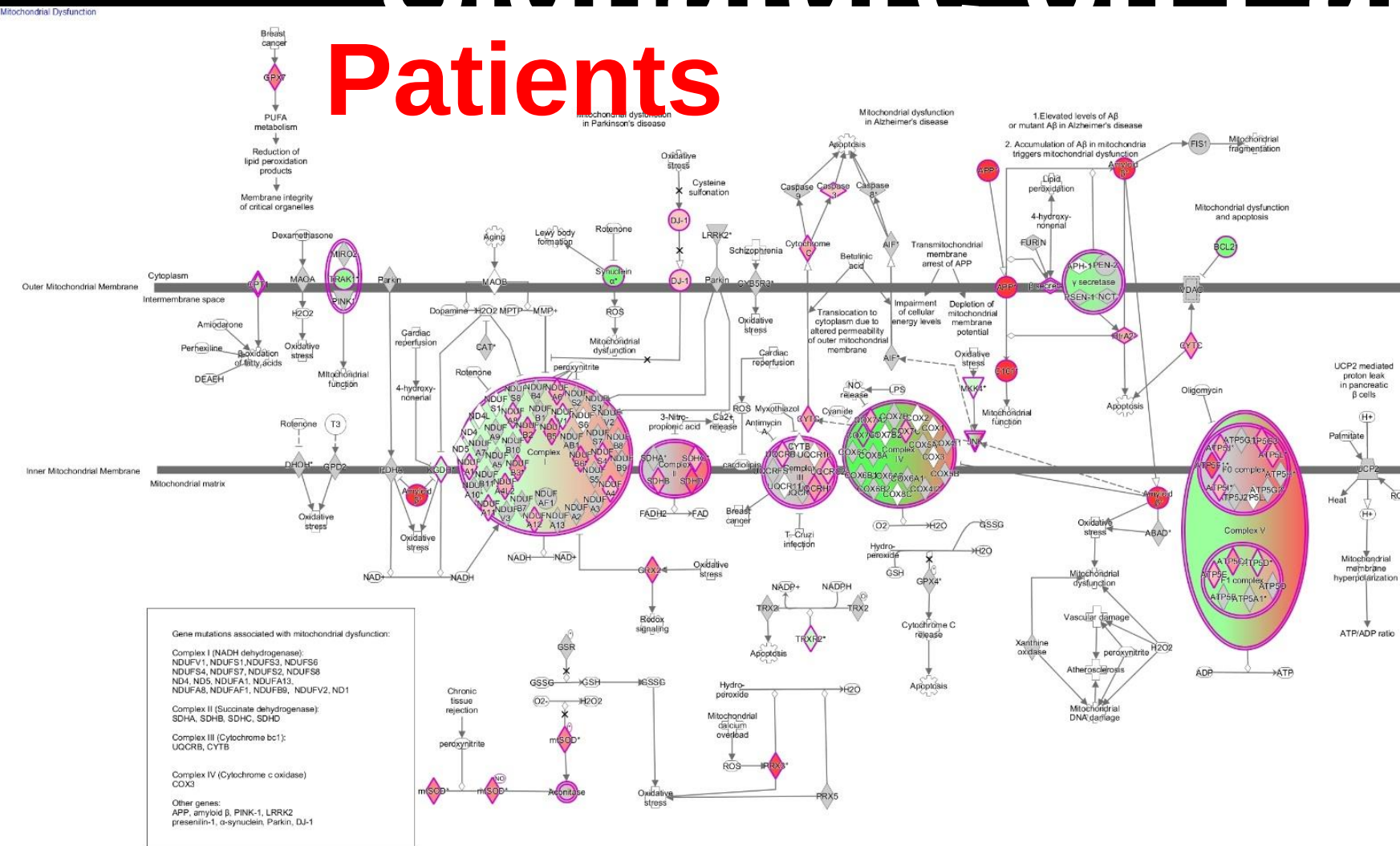
Thank you.

Metabolic Adaptation of Resistant Melanoma Tumor: GSEA

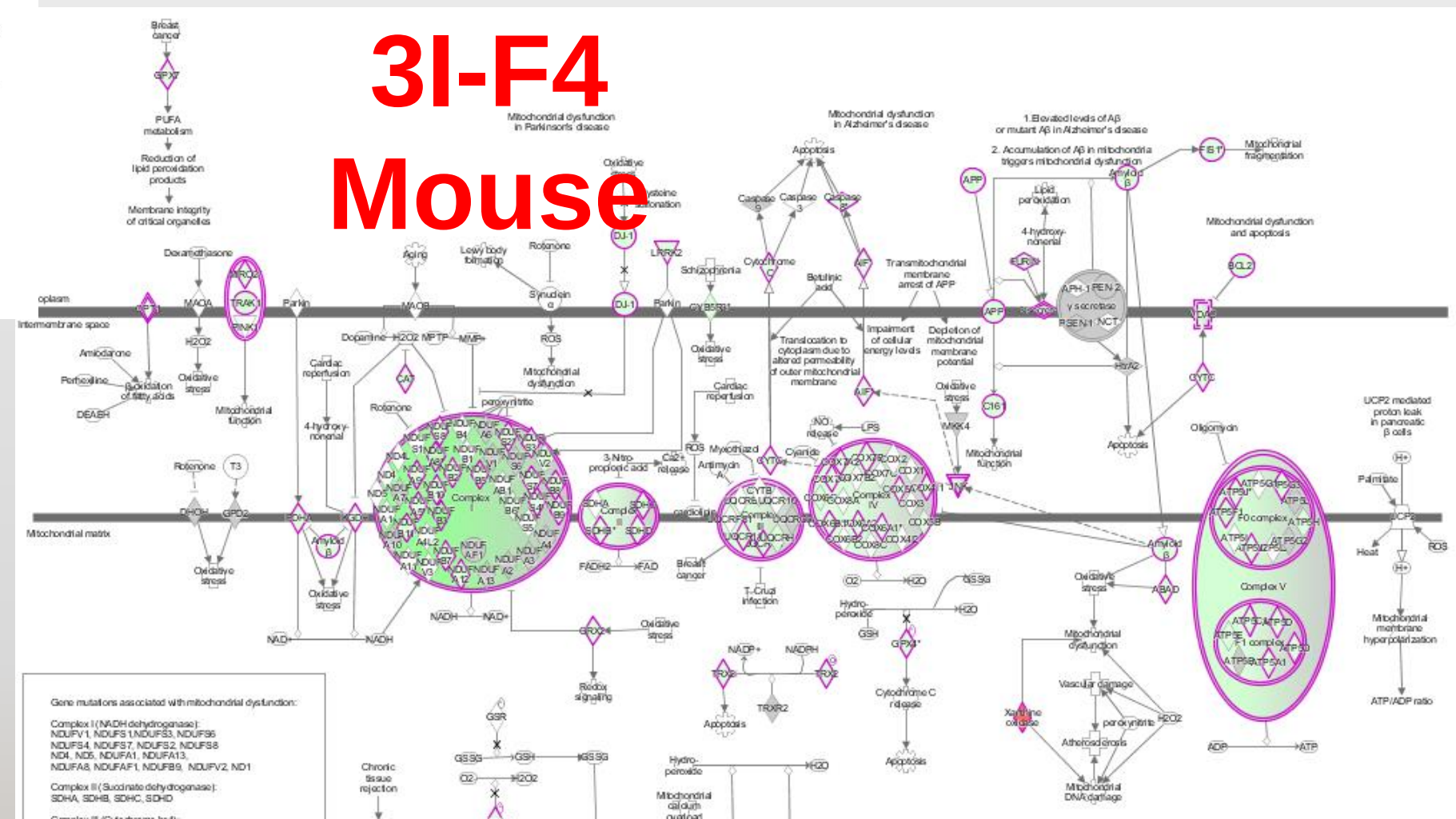


Validation of Immunotherapy Resistant Signature on Patients Sample:IPA

Patients



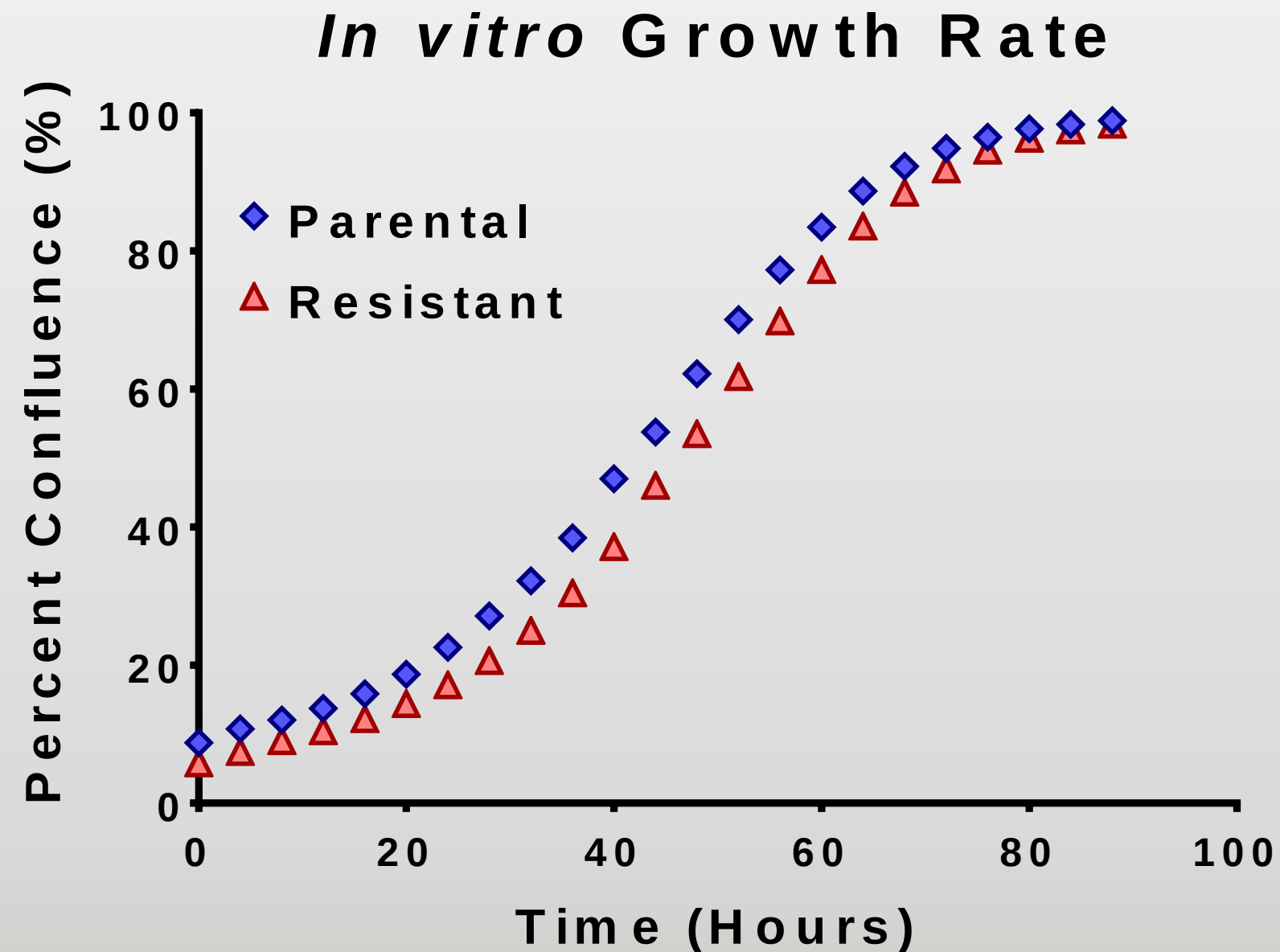
3I-F4 Mouse



Altered Oxidative Phosphorylation

Characterization of Immunotherapy Resistant Melanoma Cells

In vitro cell growth assay (incucyte)



Resistant Tumor Increased Glycolytic and TCA Cycle Metabolites: NMR Profile

