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Society for Immunotherapy of Cancer

The Roadmap to Tumor-infiltrating Lymphocyte (TIL) Therapy: Understanding Genetic Alterations for Improved Patient Treatment

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Bernatchez Lab

11/10/2019

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

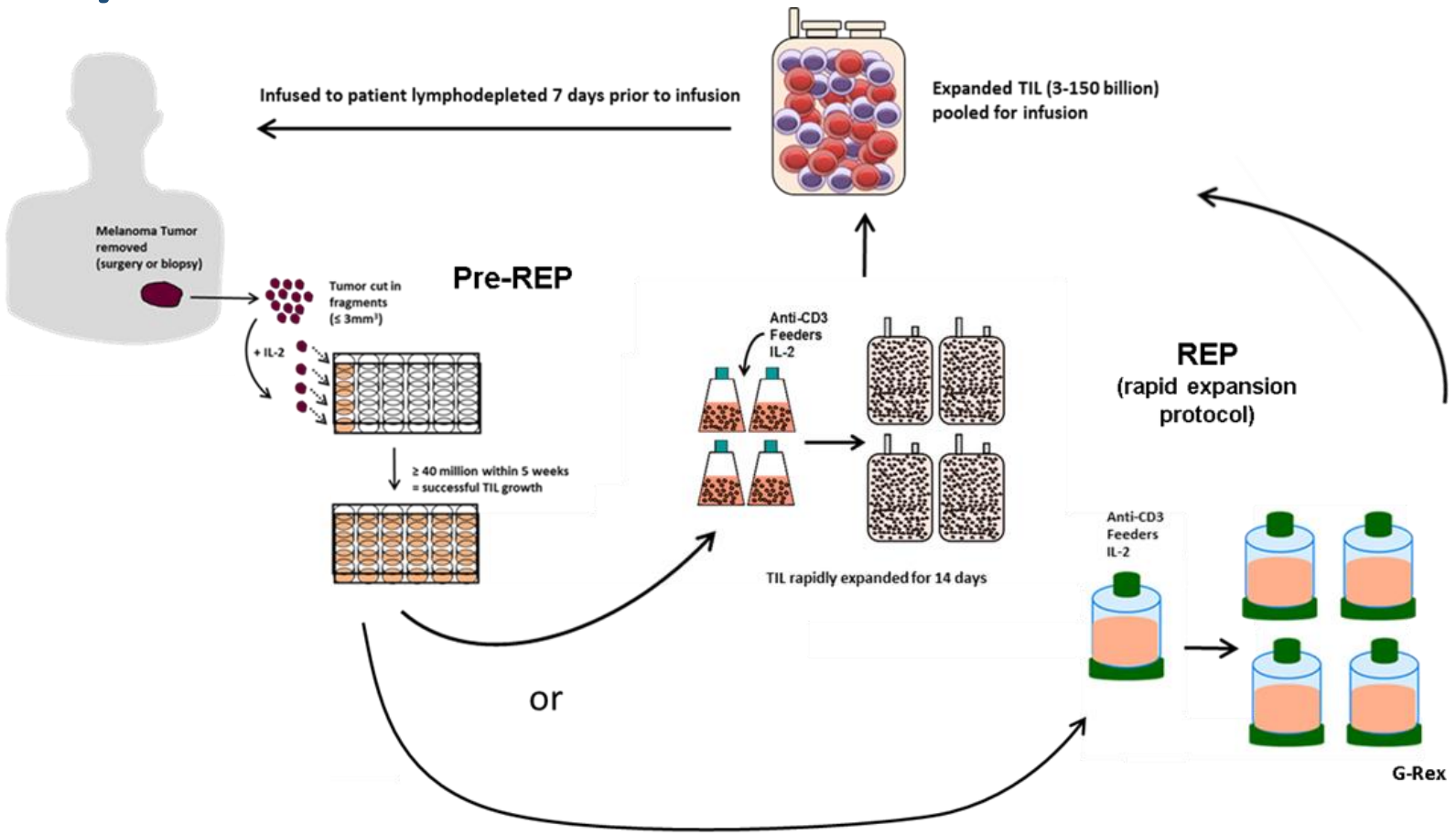
Presenter Disclosure Information

Caitlin Creasy

The following relationships exist related to this presentation:

No relationships to disclose

Adoptive Cell Transfer of Tumor-Infiltrating Lymphocytes at UTMDACC



Adapted from Tavera, Forget et al., *Journal of Immunotherapy* 2018

Clinical response to TIL therapy for metastatic melanoma worldwide

MDACC (USA)

Number of Patients	CR	PR	CR + PR (%)
74	8	23	31 (42%)

Number reported in Forget, Haymaker et al. 2018, Clinical Cancer Research

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Moffit Cancer Center (USA)

Number of Patients	CR	PR	CR + PR (%)
13	2	3	5 (38%)

Number reported in Pilon-Thomas et al. J. Immunother 2012

NCI (USA)

Number of Patients	CR	PR	CR + PR (%)
93	20	32	52 (56%)

Number reported in Rosenberg et al. Clin Can Res 2011

Sheba (Israel)

Number of Patients	CR	PR	CR + PR (%)
57	5	18	23 (40%)

Number reported in Besser et al. Clin Can Res 2013

University of Copenhagen (Denmark)

Number of Patients	CR	PR	CR + PR (%)
24	3	7	10 (42%)

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Question: Why do 50% of patients not respond to therapy?

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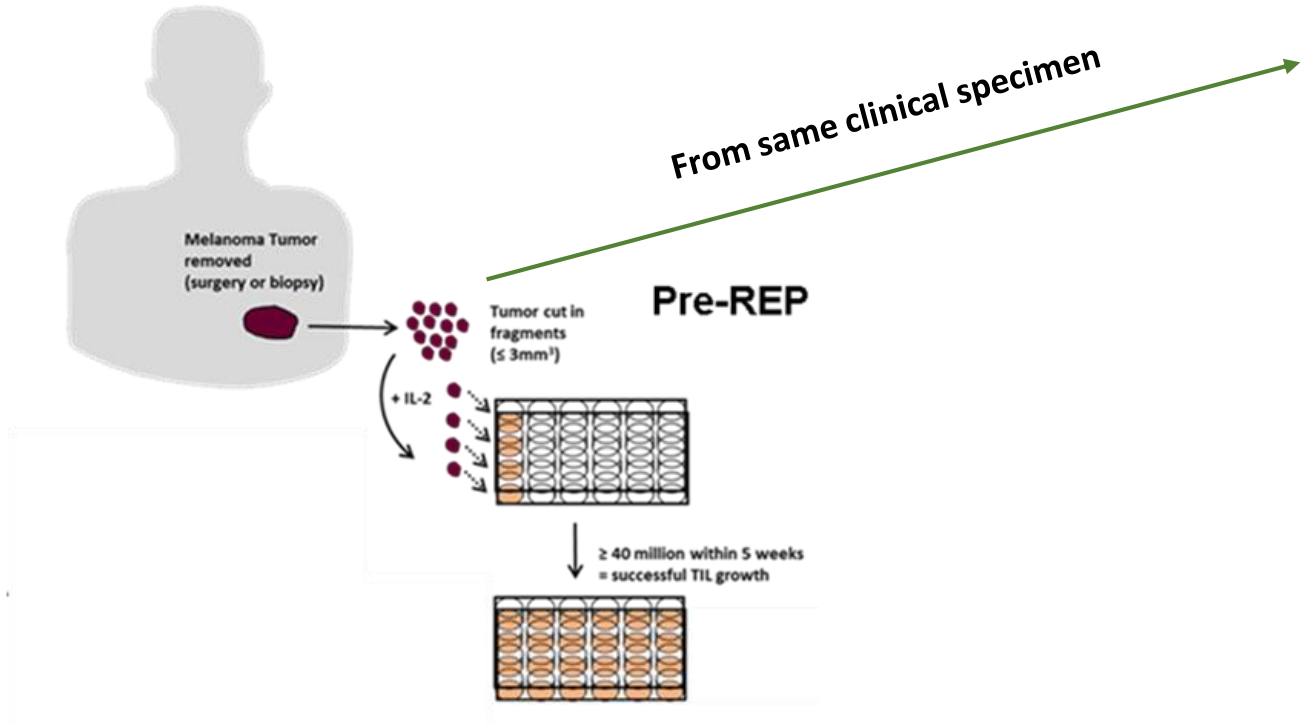
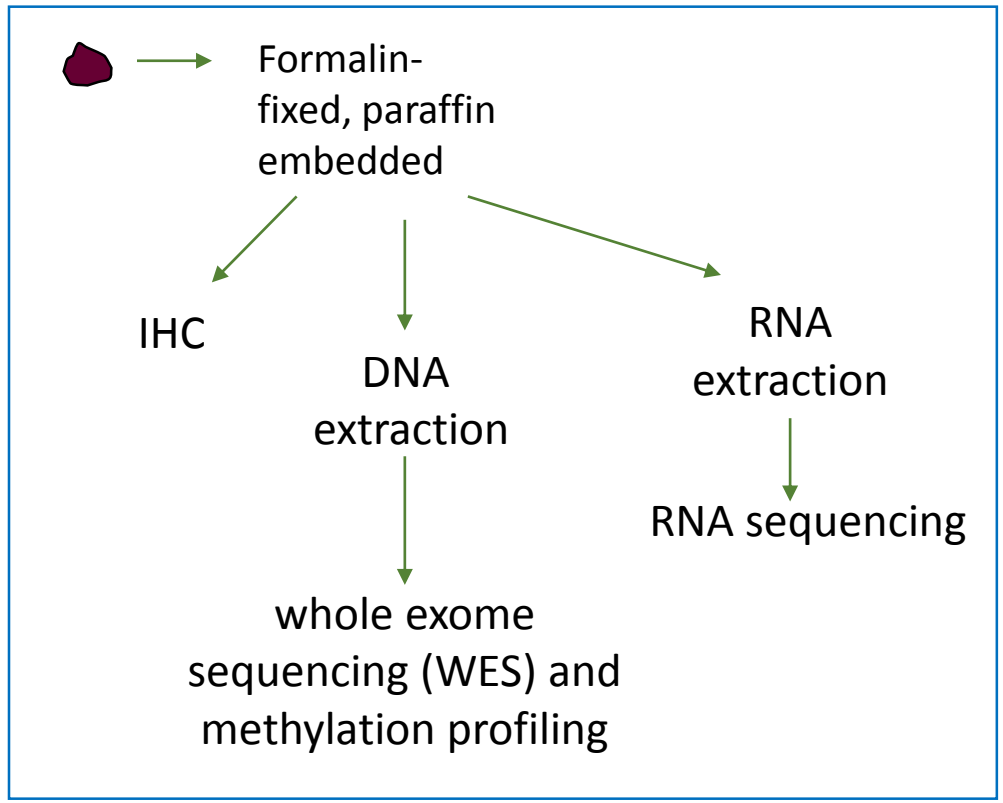
Using formalin-fixed, paraffin embedded (FFPE) patient tissues to investigate genetic differences





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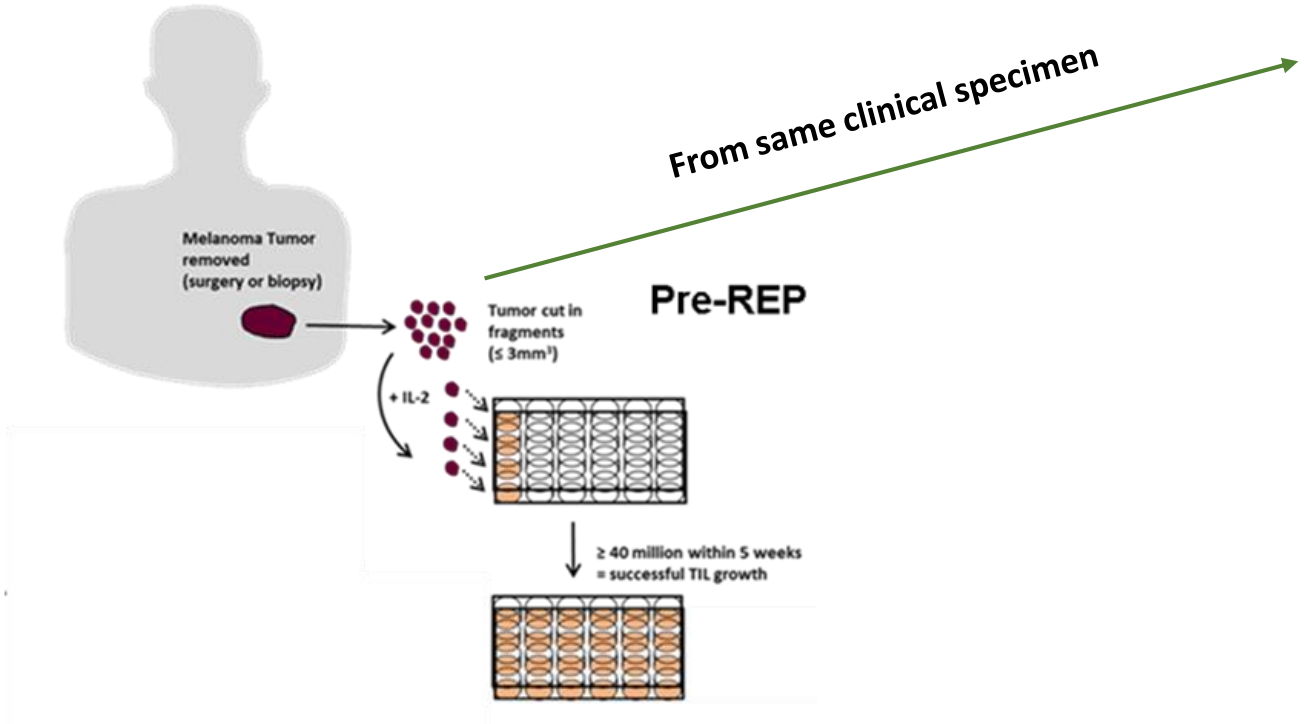
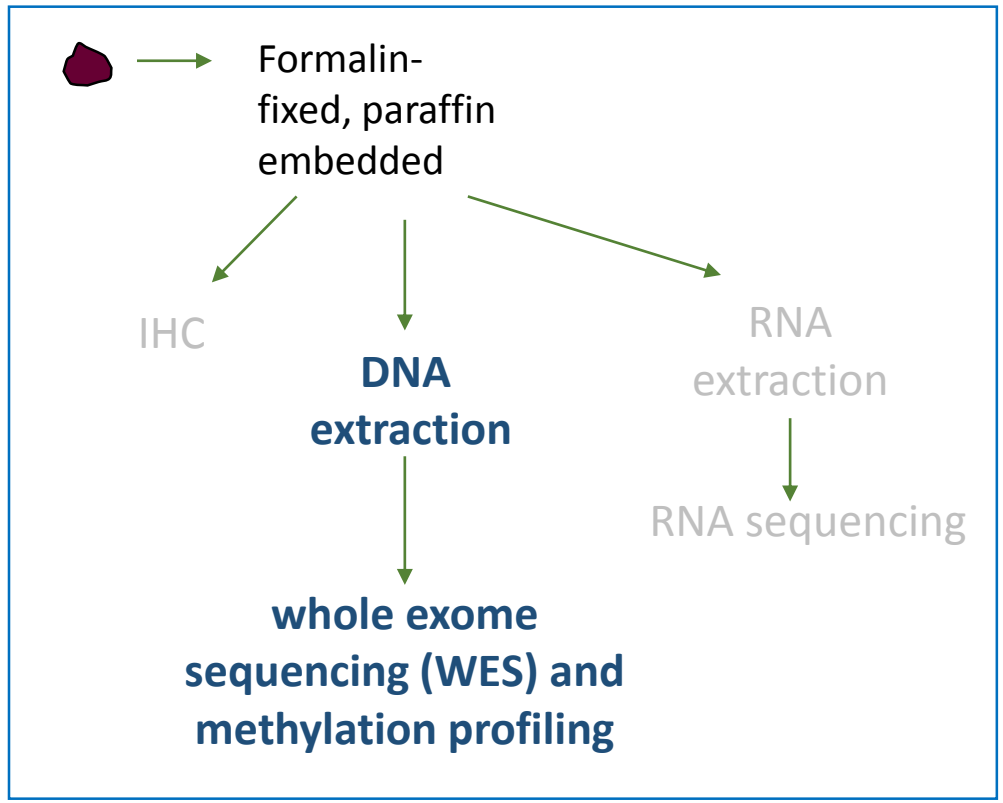




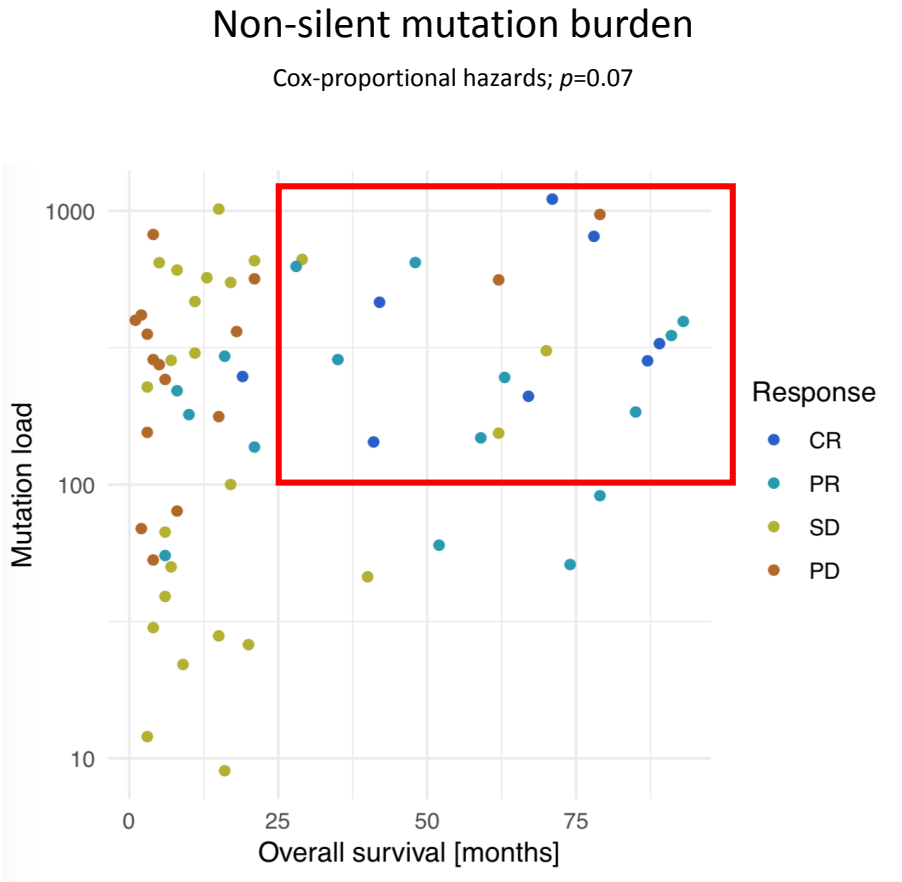
Adapted from Tavera, Forget et al., *Journal of Immunotherapy* 2018

Profile of Patient Samples used for WES

- 61 patients treated at MDACC
- 9 patients treated at Moffitt Cancer Center

Number of patients		Total	Complete Responder	Partial Responder	Stable Disease	Progressive Disease	Progressed Sample
Stage							
	IIIC	4	2	1	1	0	0
Stage IV	M1a	1	0	0	0	1	0
Stage IV	M1b	10	1	1	5	2	1
Stage IV	M1c	55	5	14	18	13	5
TIL Harvest Site							
	Lymph Node	19	3	2	7	6	1
	Soft Tissue	31	0	9	13	5	4
	Visceral	10	3	2	2	2	1
	Metastasis Soft Tissue+ Visceral	1	0	1	0	0	0
	Lymph Node+ Visceral	3	1	1	1	0	0
	Soft Tissue+ Lymph Node	6	1	1	1	3	0
Progression on TIL							
	Yes	59	2	11	24	16	6
	No	11	6	5	0	0	0

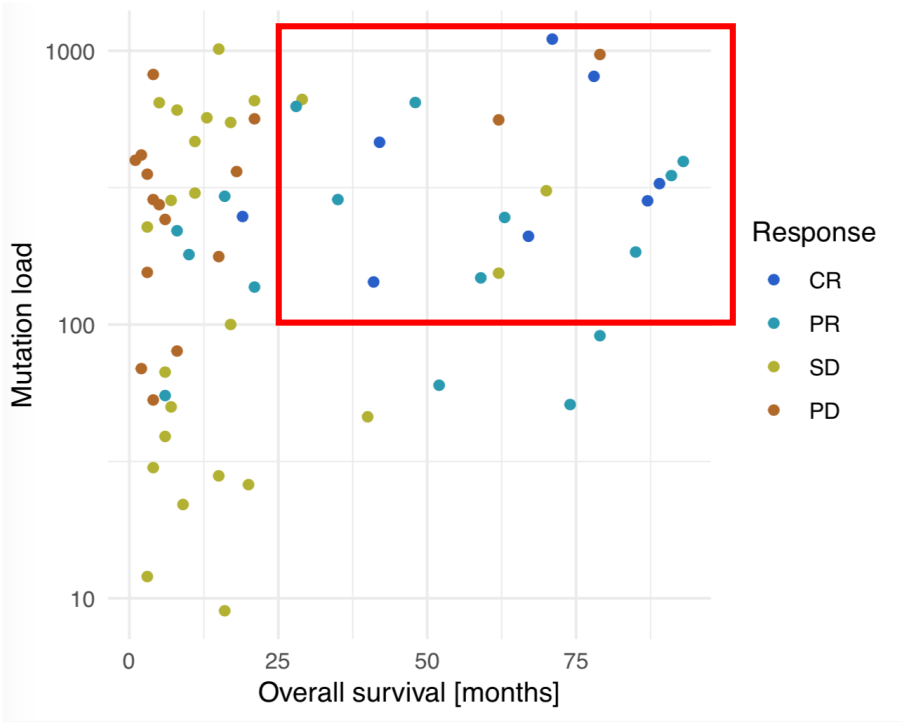
Higher Non-Silent Mutation Burden AND Neo-Antigen load associate with OS after TIL therapy



Higher Non-Silent Mutation Burden AND Neo-Antigen load associate with OS after TIL therapy

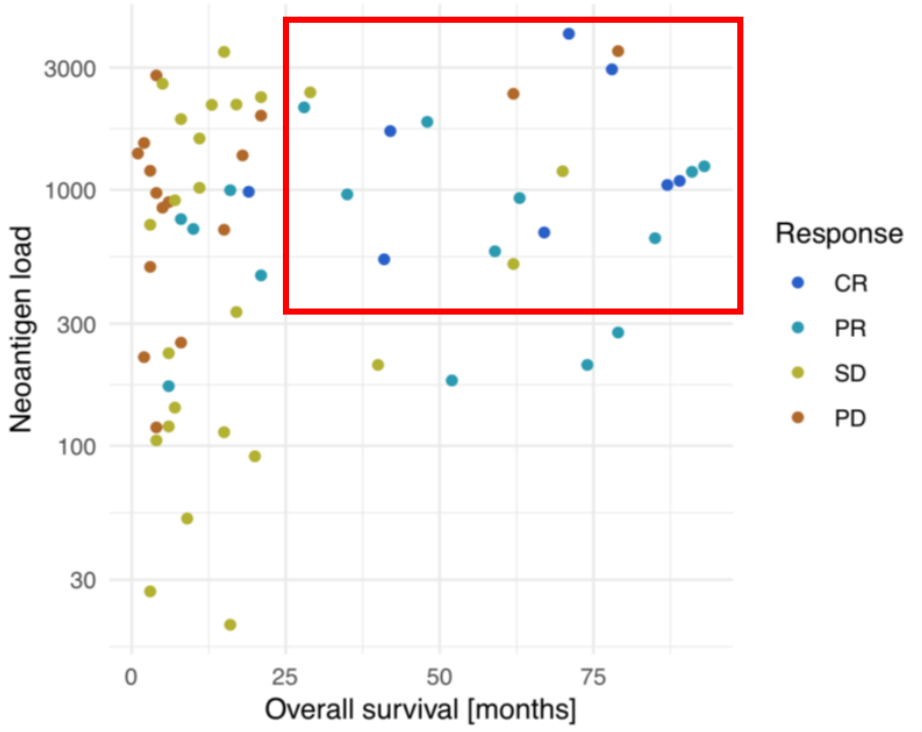
Non-silent mutation burden

Cox-proportional hazards; *p*=0.07

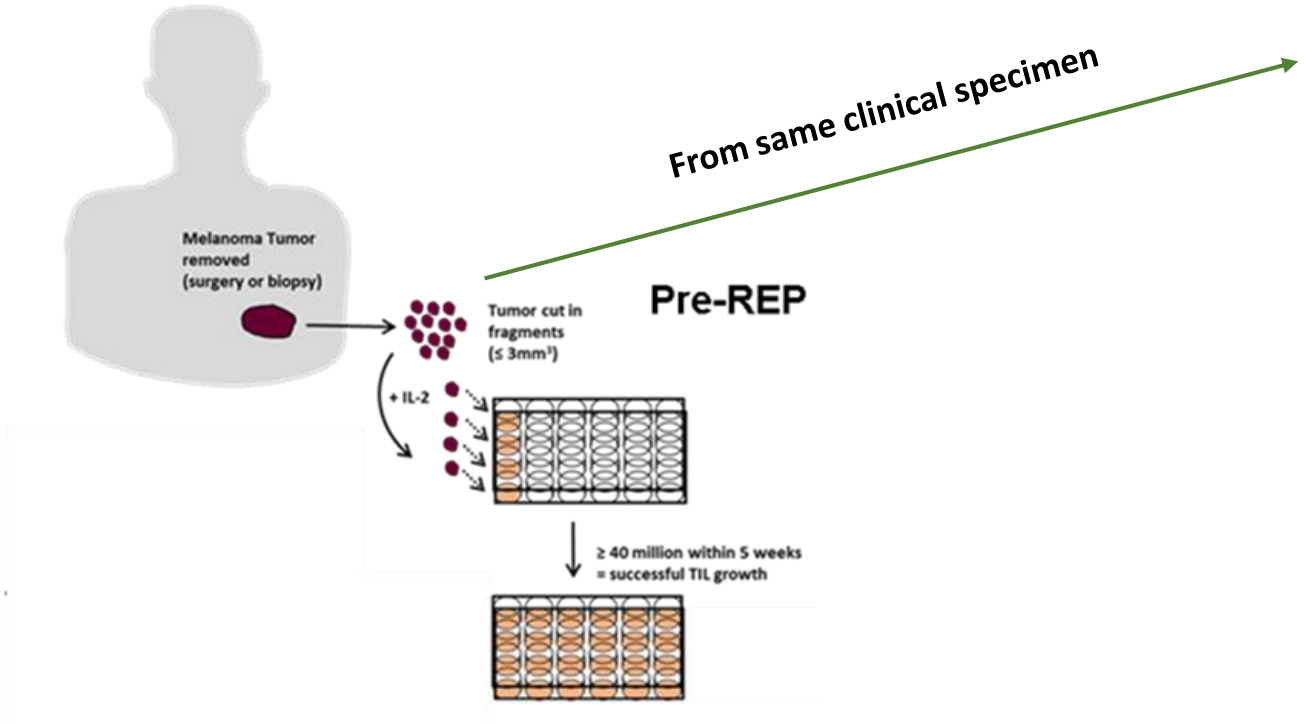


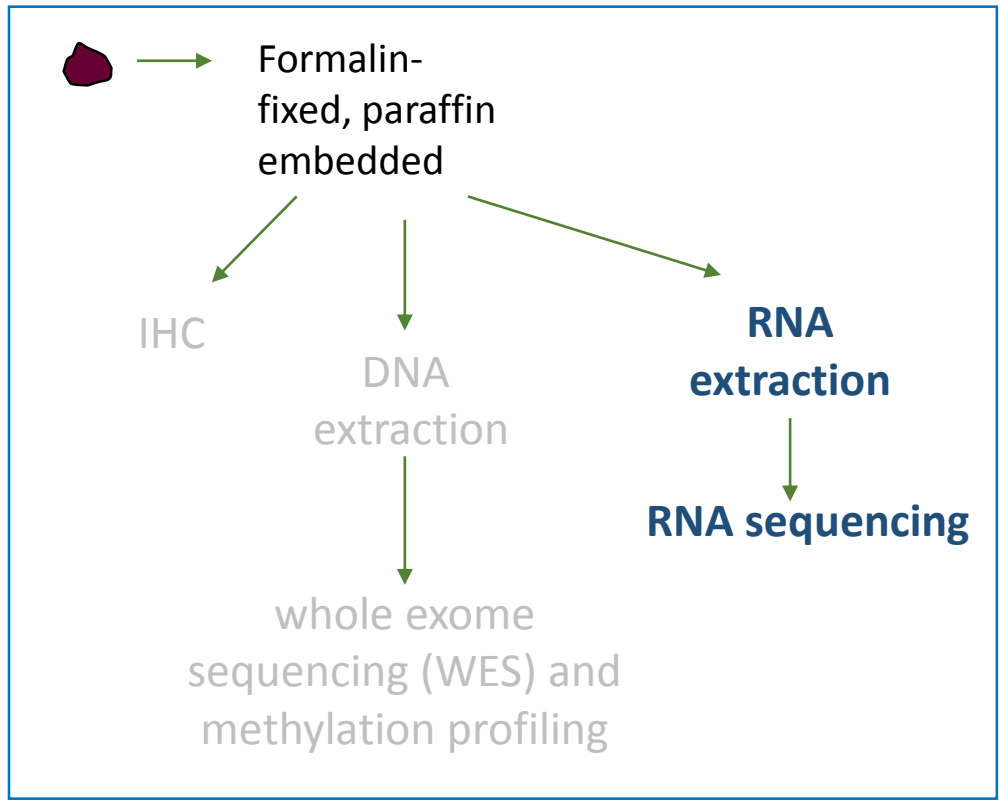
Neoantigen burden

Cox-proportional hazards; *p*=0.042



Using formalin-fixed, paraffin embedded (FFPE) patient tissues to investigate genetic differences





Adapted from Tavera, Forget et al., *Journal of Immunotherapy* 2018

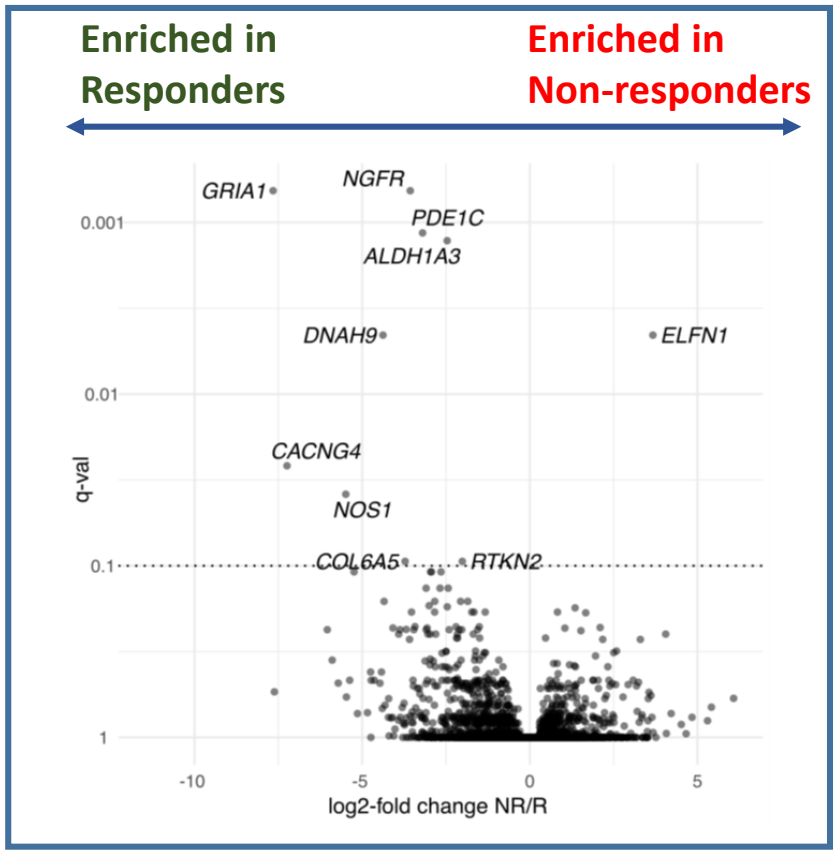
Profile of Patient Samples used for RNA sequencing

- 42 patients treated at MDACC

Number of patients		Total	Complete Responder	Partial Responder	Stable Disease	Progressive Disease	Progressed Sample
Stage							
	IIIC	2	0	0	1	0	1
Stage IV	M1a	1	0	0	0	1	0
Stage IV	M1b	4	0	2	2	0	0
Stage IV	M1c	35	2	5	14	7	7
TIL Harvest Site							
	Lymph Node	12	1	1	3	6	1
	Soft Tissue	19	0	5	9	1	4
	Visceral	5	0	1	2	0	2
	Metastasis Soft Tissue+ Visceral	0	0	0	0	0	0
	Lymph Node+ Visceral	3	1	0	1	0	1
	Soft Tissue+ Lymph Node	3	0	0	2	1	0
Progression on TIL							
	Yes	38	0	5	17	8	8
	No	4	2	2	0	0	0

RNA sequencing reveals differences in genes enriched in response and survival

Response

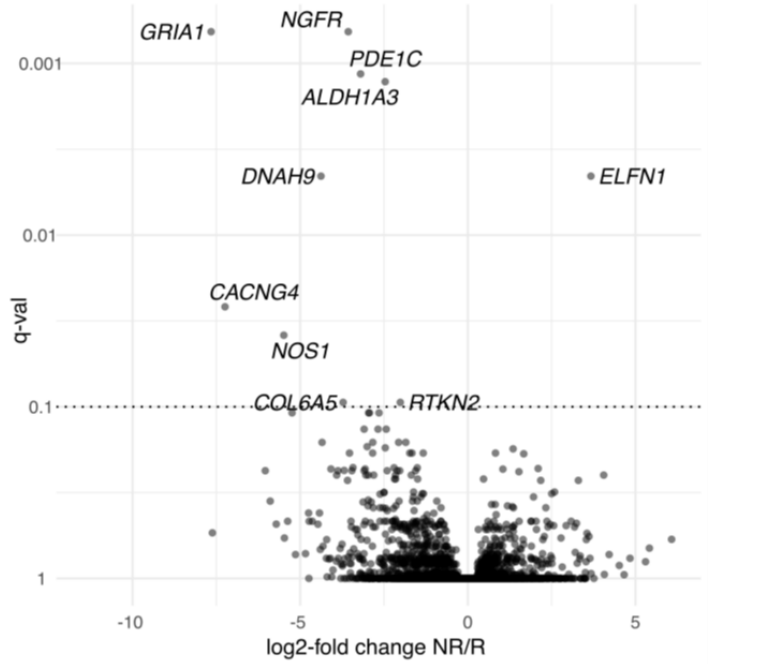


Samples labeled have a q<0.01

RNA sequencing reveals differences in genes enriched in response and survival

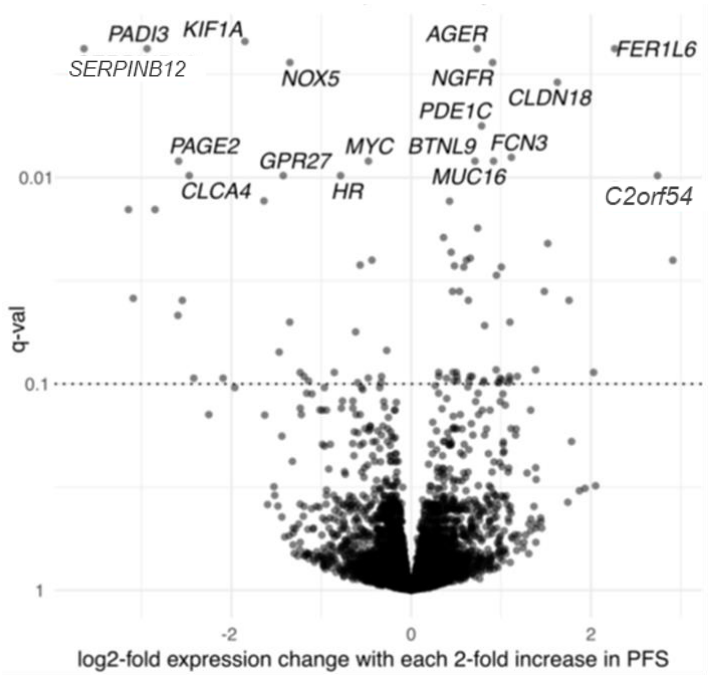
Response

Enriched in Responders ⟷ **Enriched in Non-responders**



PFS

Enriched in Short PFS ⟷ **Enriched in Long PFS**



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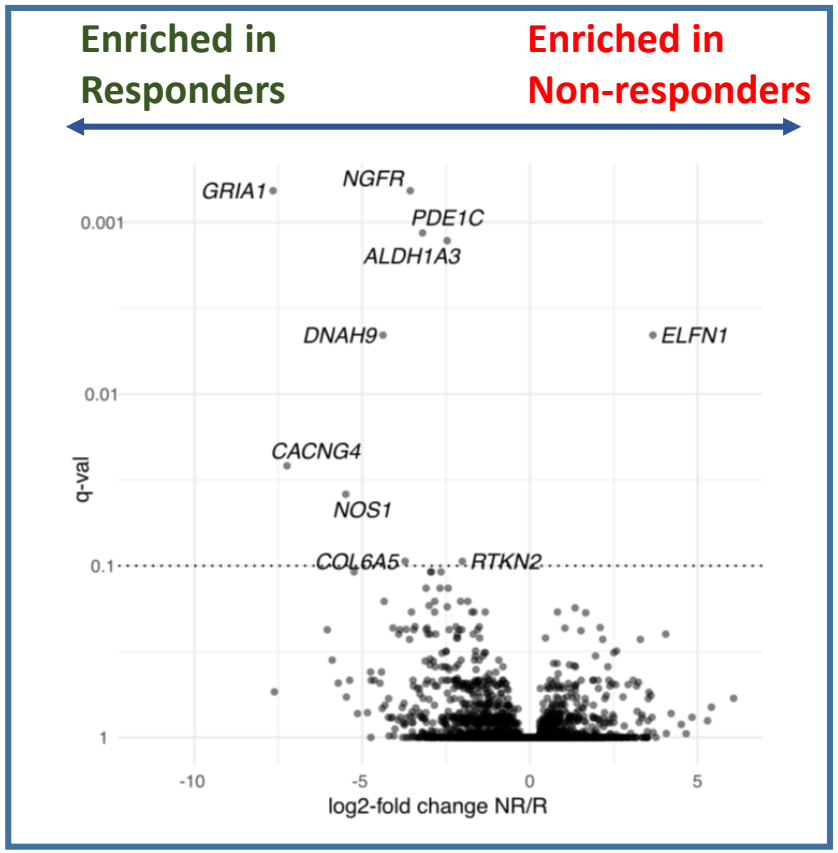
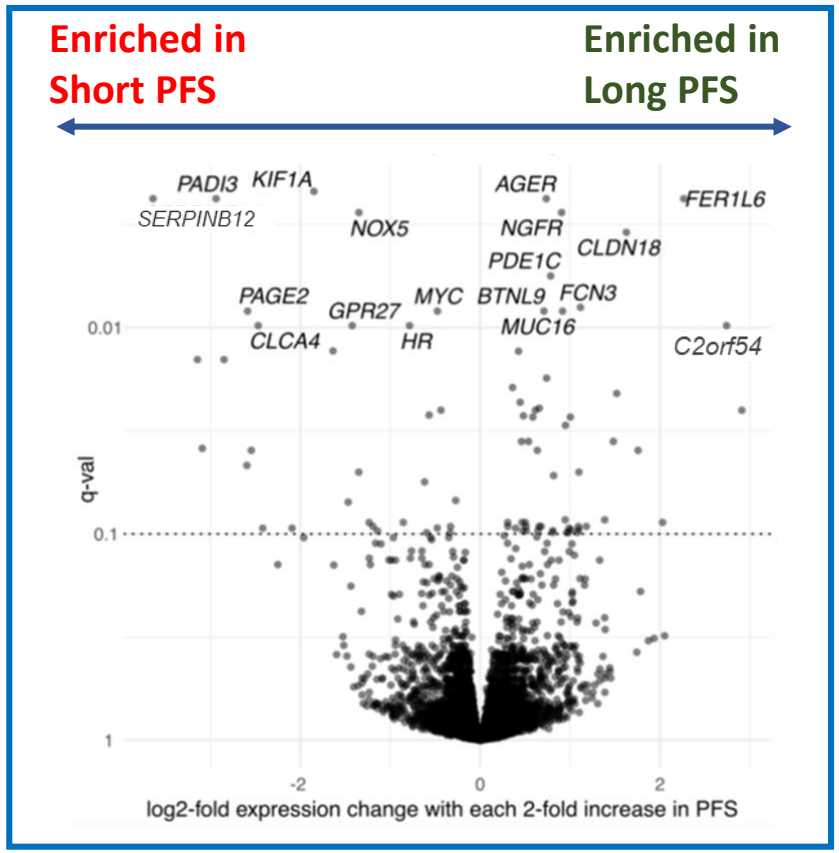
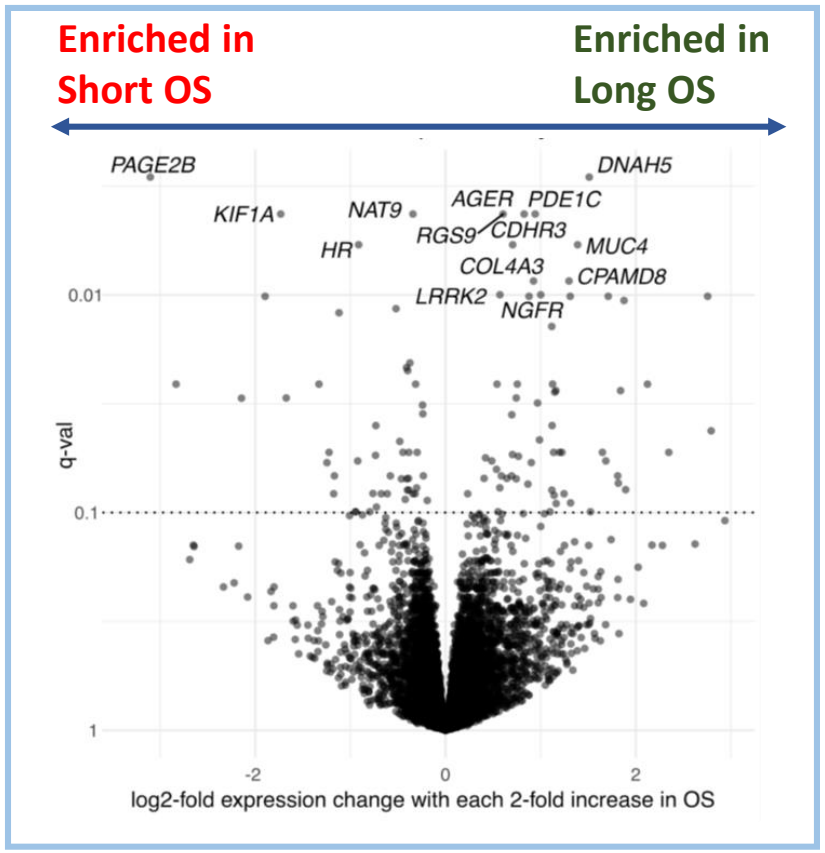


PFS



OS



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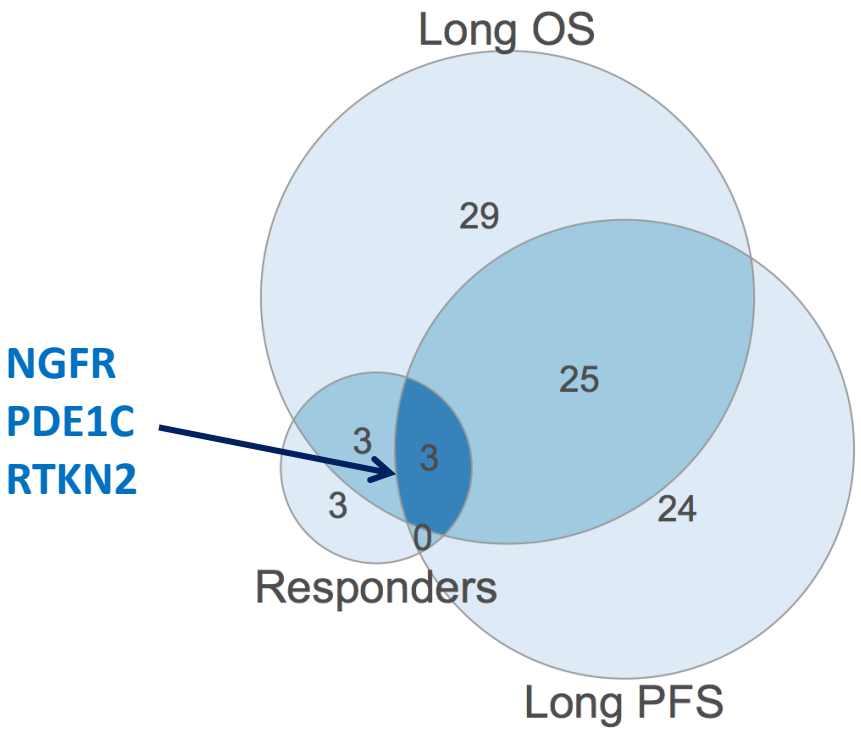
Genes consistently enriched across OS, PFS and response

- The overlap between the OS, PFS, and response is very significant ($p<0.003$ pairwise Fisher exact tests)

- We compared genes that were associated with all 3 outcomes



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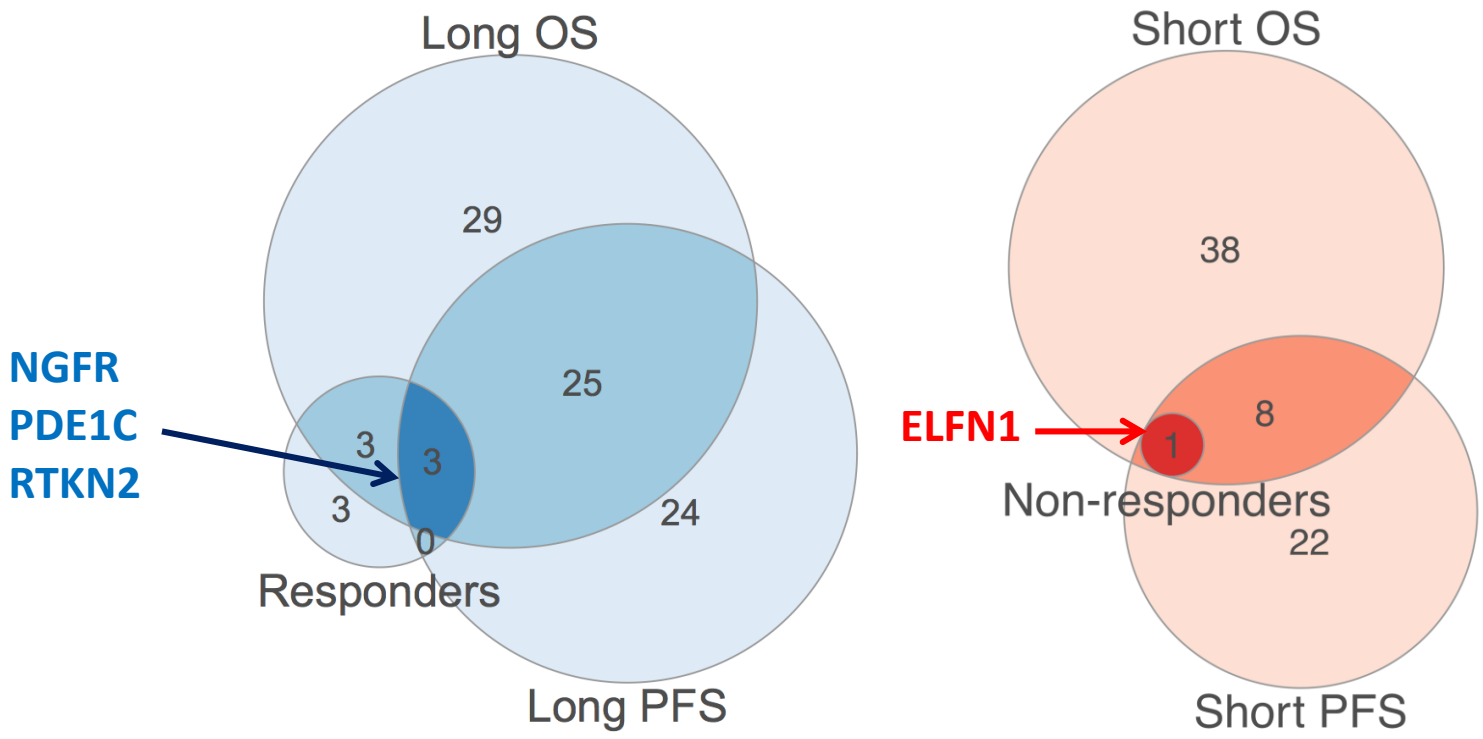

Genes consistently enriched across OS, PFS and response

Associated with improved survival and response: PDE1C, NGFR, and RTKN2

- **PDE1C**- Phosphodiesterase 1C
  - inhibits cAMP and cGMP (Shimizu et al., 2009)
  - cAMP negatively regulates T_{eff} cells (Wehbi and Taskén, 2016)
- **RTKN2**- Rhotekin 2
  - Apoptosis occurs in $CD4^+$ cells lacking RTKN2 (Collier et al., 2008)
- **NGFR**- Nerve growth factor receptor
  - Enriched as melanoma progresses and metastasizes (Radke et al., 2017)
  - NGFR can bind to B7-1 (AAI 2019 Abstract, Morano et al., 2019)

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Associated with poor survival and no response: ELFN1

- **ELFN1**- Extracellular Leucine Rich Repeat and Fibronectin Type III Domain Containing 1
  - inhibits glutamate receptor type 3 (Dunn et al., 2018)
  - T cells cannot be activated or have proper migration without glutamate (Shanker et al., 2018)

ELFN1 Methylation Supports Distinct Profiles in Response to ACT

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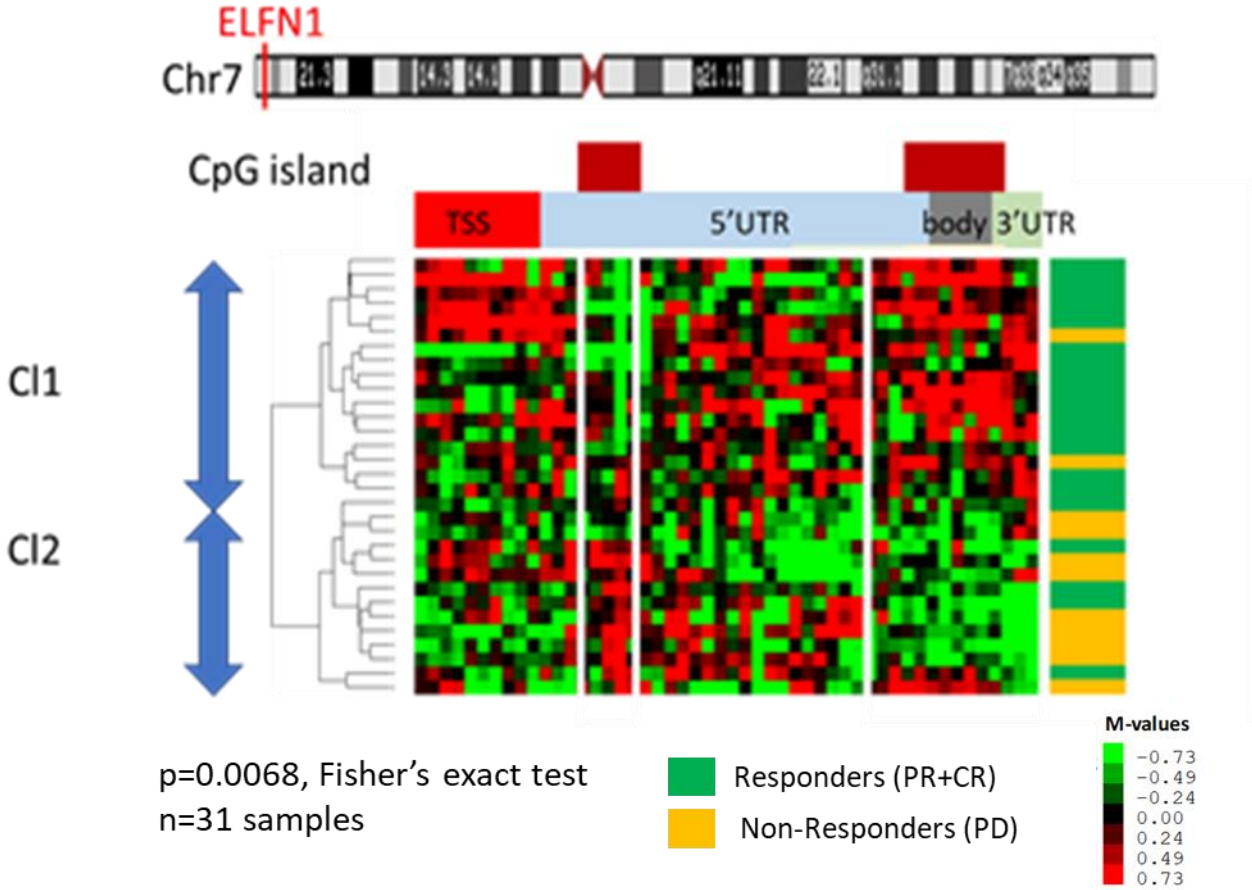
  - inhibits glutamate receptor type 3 (Dunn et al., 2018)
  - T cells cannot be activated or have proper migration without glutamate (Shanker et al., 2018)
- Hyper-methylation supports low expression of ELFN1 in responding patients
- Hypo-methylation suggests gene expression of ELFN1 in non-responding patients



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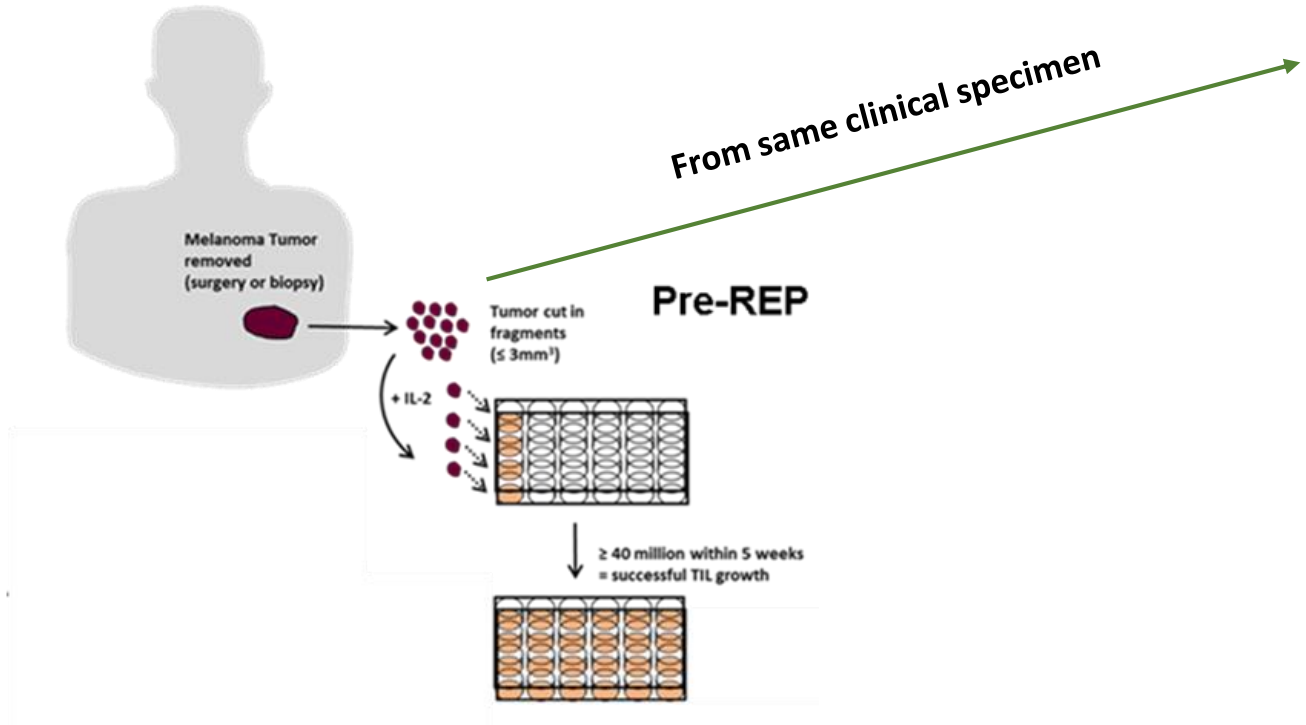

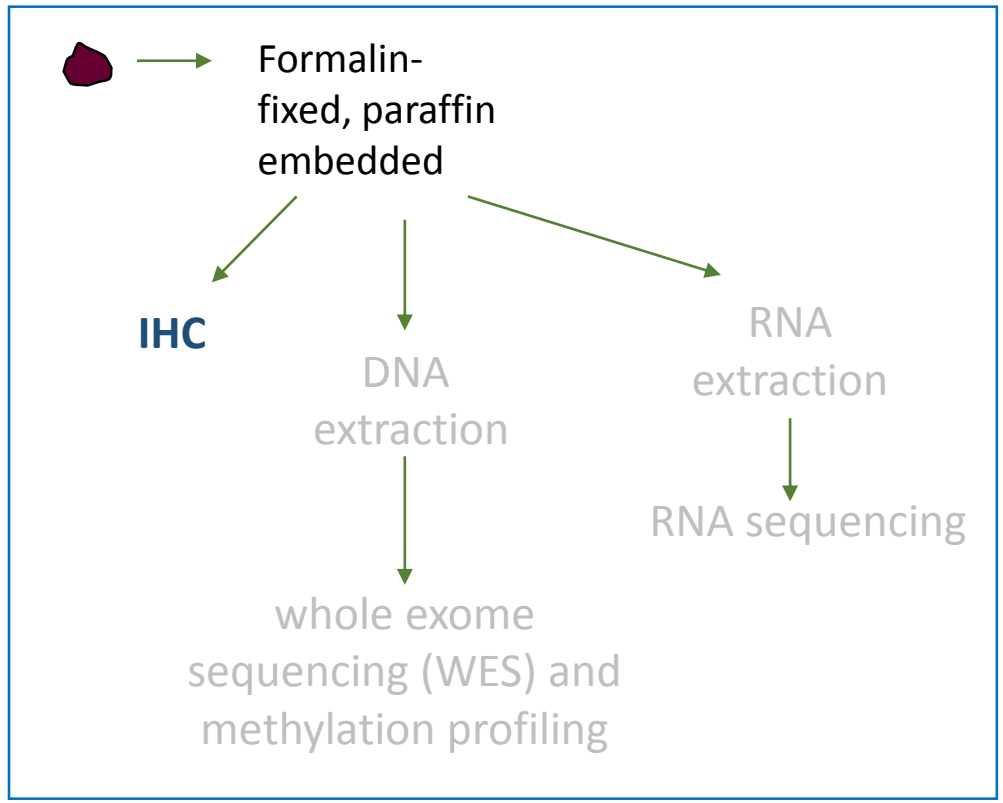

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ELFN1 is expressed in tumor cells of metastatic melanoma patients

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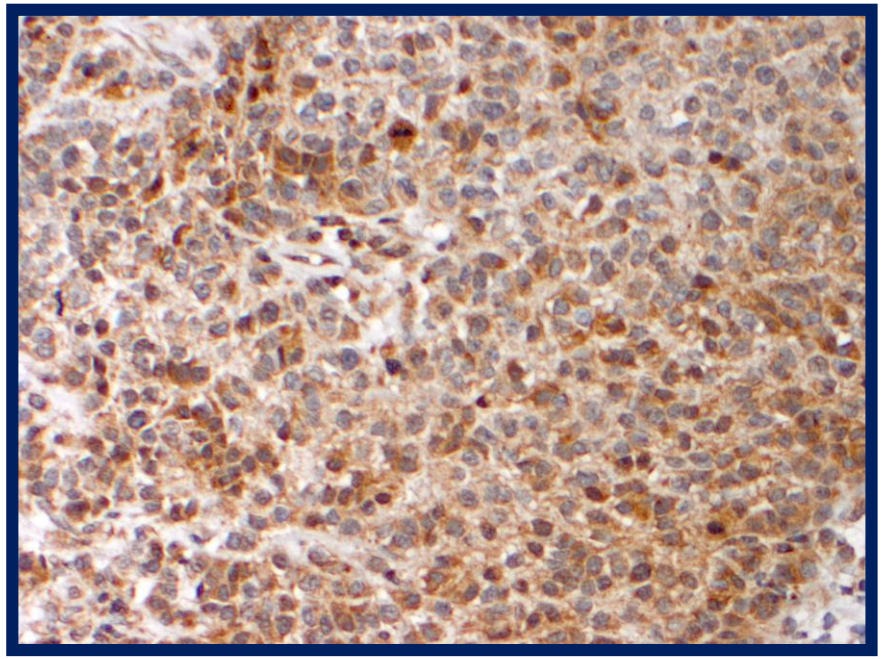
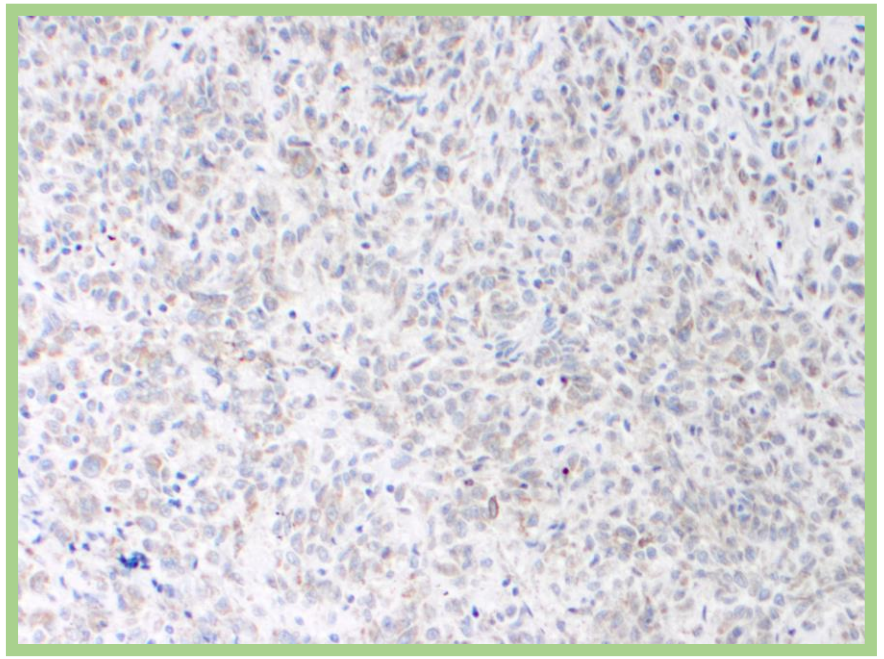


Patient Sample 1

+

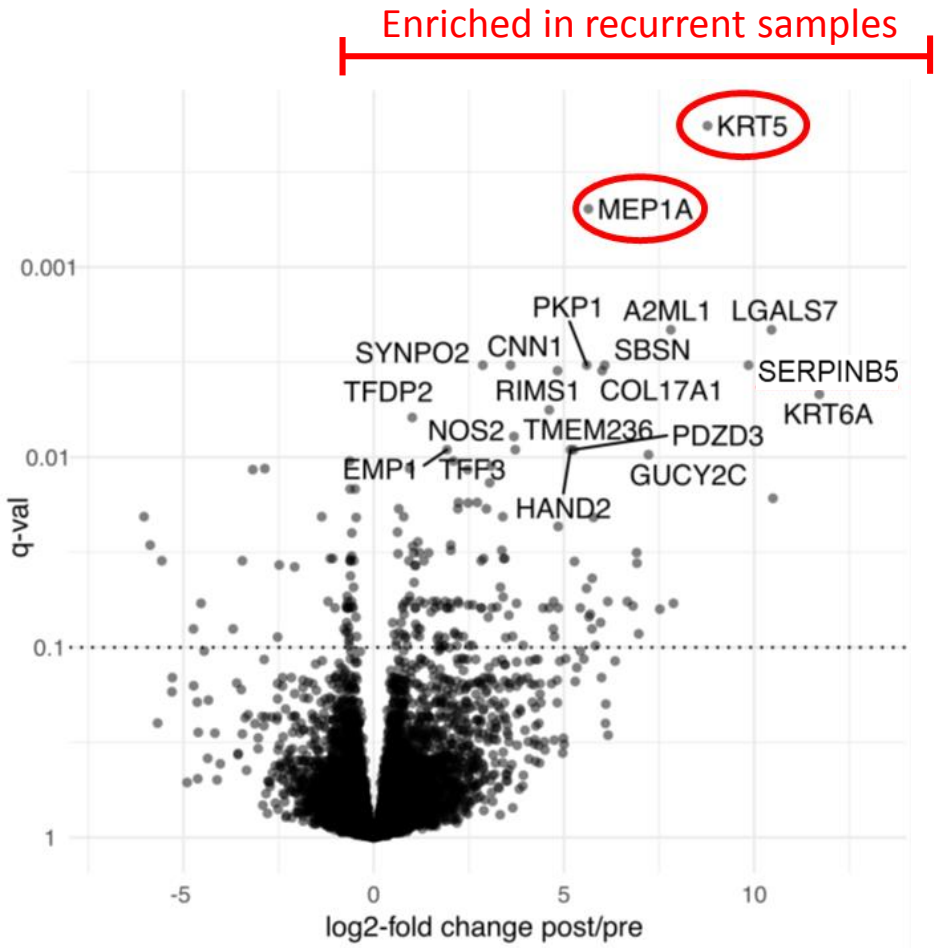


Patient Sample 2

200x Magnification
Brown: represents ELFN1 and
Counterstained: Hematoxylin

Differentially expressed genes at recurrence

- 8 cases of post-TIL ACT at MDACC
  - 3 paired cases
- Enriched genes at recurrence associate with an EMT-like phenotype



Conclusions and Take Home Messages

- Conclusions
  - Enriched non-silent mutation burden and neo-antigen load associate with overall survival after TIL therapy, but not PFS or response
  - RNA sequencing reveals PDE1C, NGFR, and RTKN2 enriched in patients with long OS, long PFS, and response
  - ELFN1 is demonstrated to be enriched in patients with short OS, short PFS, and non-responsiveness as supported by methylation profiling.
  - There is an enrichment of genes associated with a mesenchymal phenotype at recurrence
- Future Directions
  - ELFN1 positive single cell transcriptomic profiling and functional studies are ongoing
- Application to the field
  - Potential biomarkers and routes of immune escape are revealed

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UTHealth The University of Texas Health Science Center at Houston | THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Graduate School of Biomedical Sciences

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Levi Garraway

Moffitt Cancer Center

Shari Pilon-Thomas
Amod Sarnaik

John Wayne Cancer Institute

Dave Hoon

Our Patients and their families!

*Co-first author