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San Antonio Breast Cancer Symposium®, December 4-8, 2018

Apobec3 induced mutagenesis sensitizes murine models of triple negative breast cancer to immunotherapy by activating B-cells and CD4+ T-cells.

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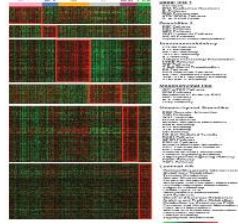
Mouse models with human TNBC-like genomic profiles

Human TNBC Subtypes

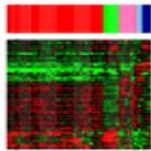


1-LAR: Luminal Androgen Receptor
2-MES: Mesenchymal
3-BLIS: Basal-like Immune Suppressed
4-BLIA: Basal-like Immune Activator

Burstein subtypes,
Burstein, CCR, 2015
(PMID:25208879)

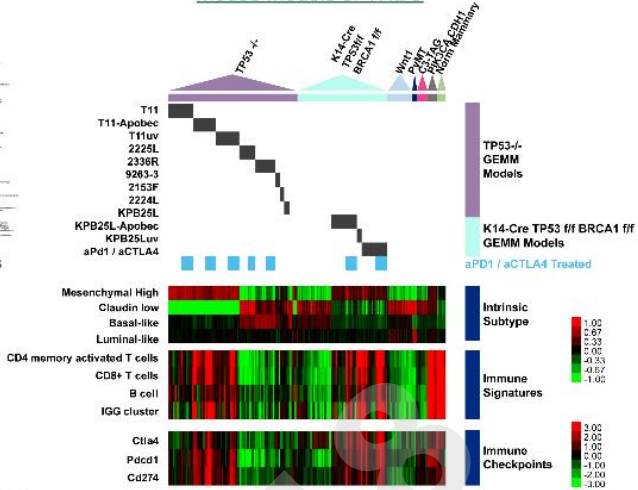


Lehmann/Vanderbilt subtypes
Lehmann et al., JCI, 2011
(PMID:21633166)



PAM50 subtypes,
Prat et al., The Oncologist, 2013
(PMID:23404817)

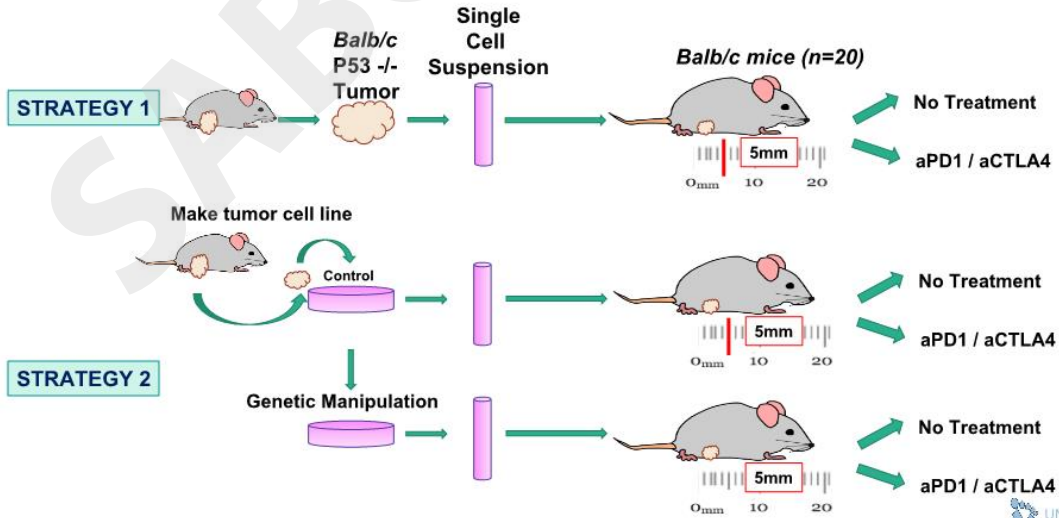
Mouse Models of TNBC



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Syngeneic Tumor Transplantation In Immune-Competent Mice

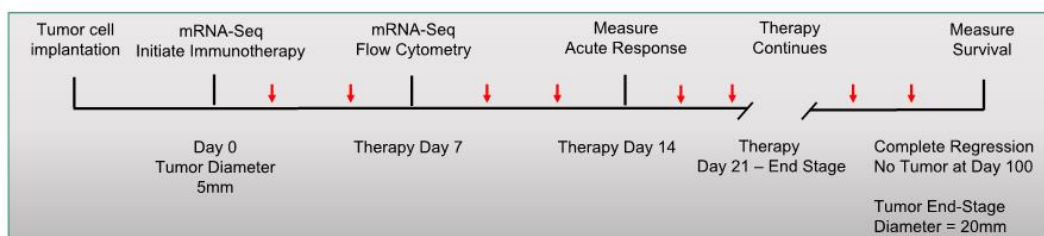


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Experimental Overview

Hypothesis: TNBC mouse models will present variable responses to immune checkpoint inhibitors, and that by using sensitive and resistant mouse models we can identify biomarkers of response

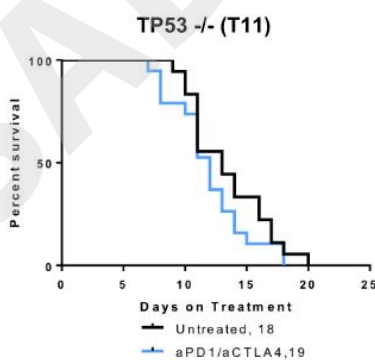


↓ Anti-PD1 = 10mg/kg + Anti-CTLA4 = .125 mg (therapy delivered twice weekly intraperitoneally)

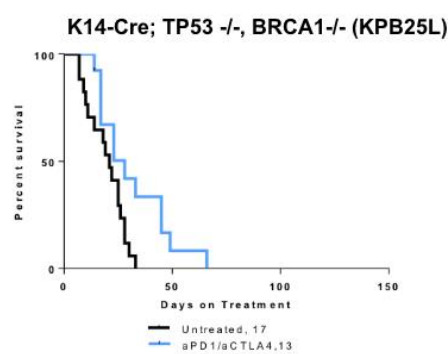
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Long-term survival for mice receiving combination immunotherapy



Model Published:
Herschkowitz et., PNAS, 2011
PMID:21633010



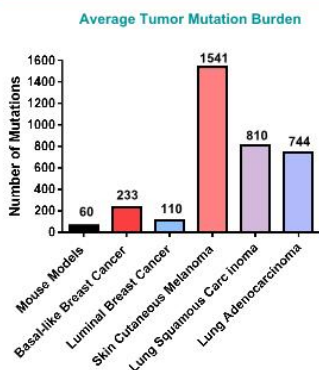
Model Published:
Hollern et al. BCRT, 2018
PMID: 30484104

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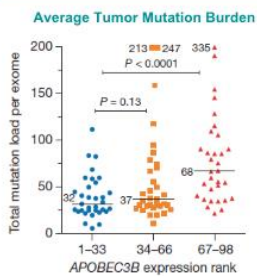


Tumor Mutation Burden

Mouse to Human Comparison

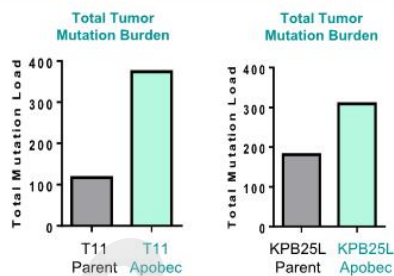


Breast Cancer Mutagenesis



Burns, Michael B., et al. "APOBEC3B is an enzymatic source of mutation in breast cancer." *Nature* 494.7437 (2013): 366.

New "Mutagenized" Mouse Models

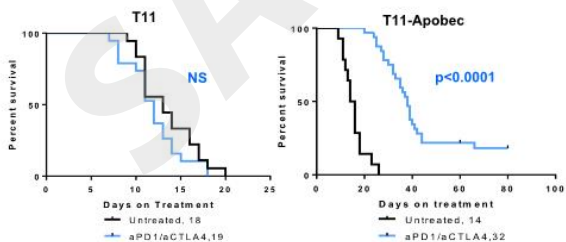


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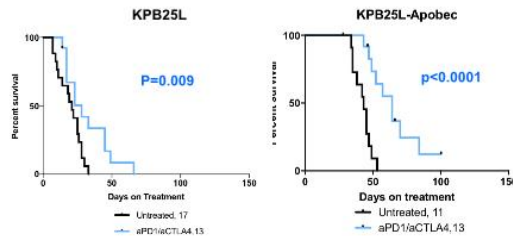


Mutation Burden and Sensitivity to Immune Checkpoint Therapy

T11 Parent / Mutagenized



KPB25L Parent / Mutagenized



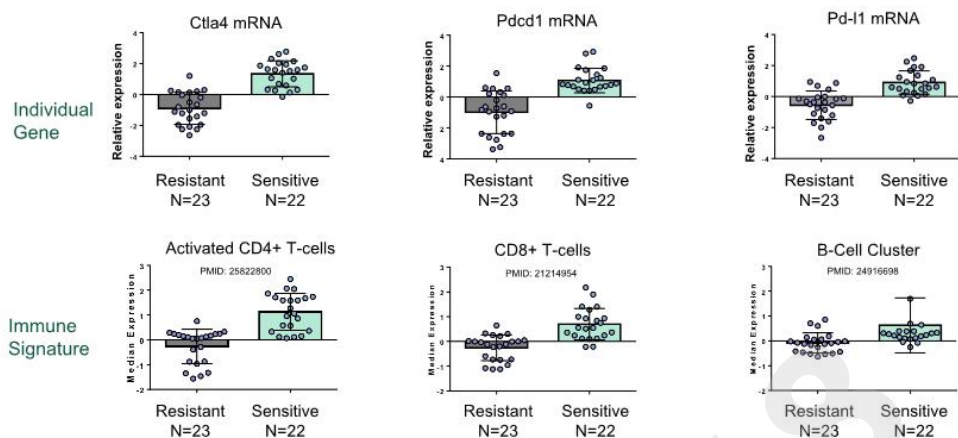
RESISTANT vs **SENSITIVE**
 6 RESISTANT MODELS TOTAL VS 5 SENSITIVE MODELS TOTAL

T11 = TP53-/-
 KPB25L = TP53-/- BRCA1 -/-

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Genomic features associated with response to immunotherapy

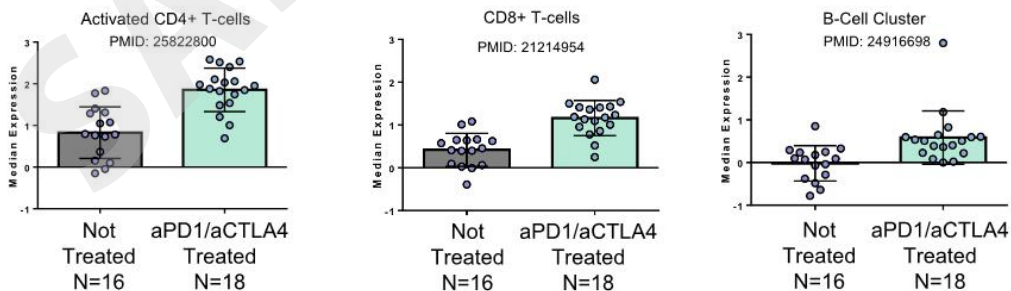


***All results p<.001

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Immune signature changes with response to immunotherapy after 7 days of therapy in sensitive models

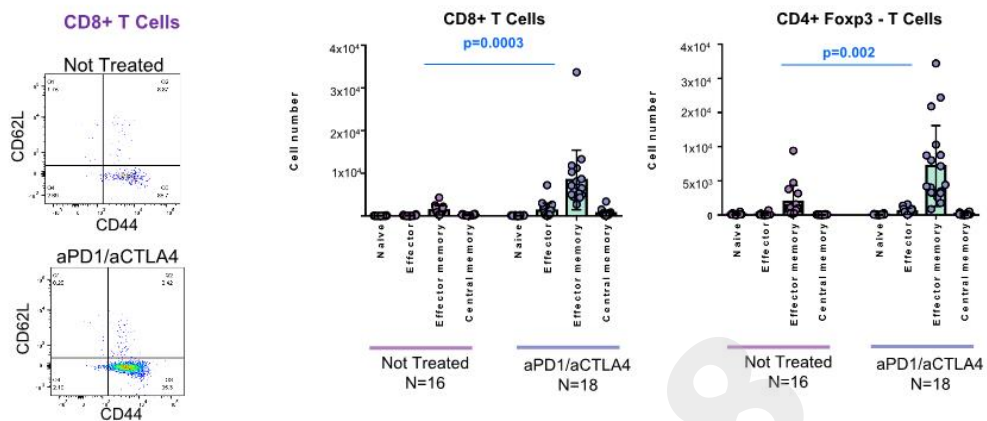


***All results p<.001

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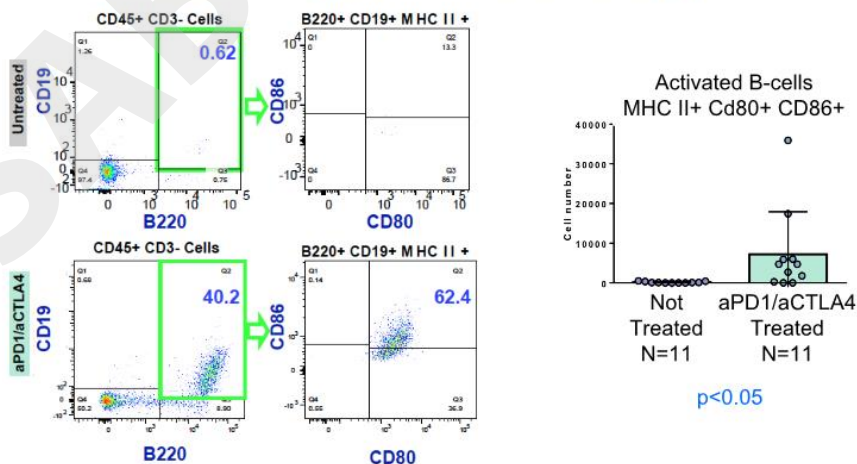
Flow cytometry analysis of T cells in sensitive models after 7 days of immunotherapy



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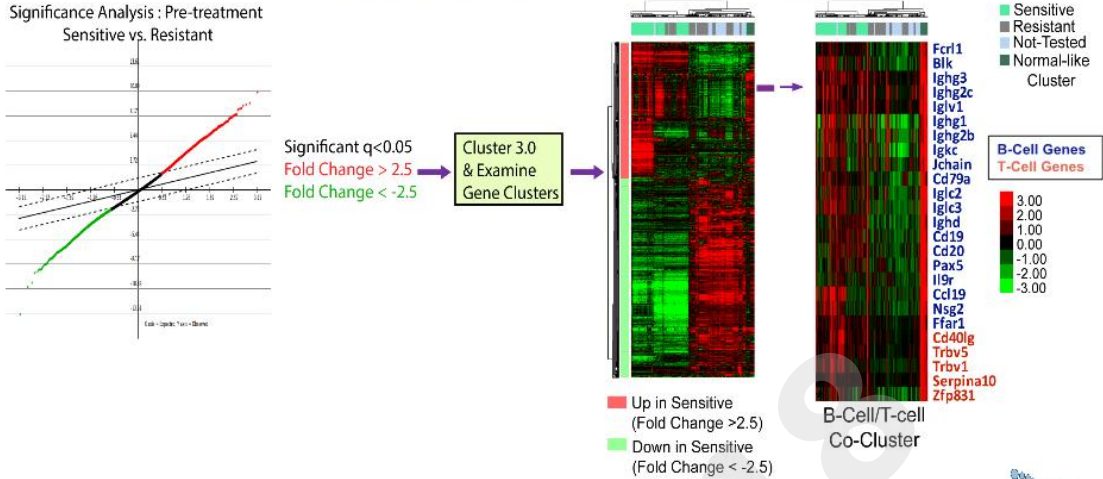
Flow cytometry analysis of B cells in sensitive models after 7 days of immunotherapy



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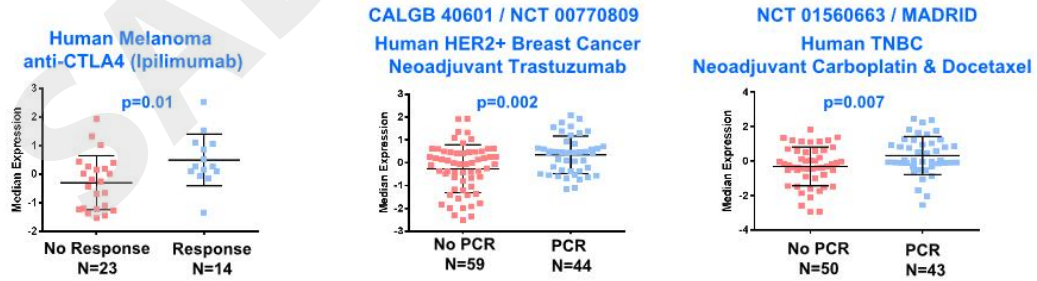
Creating New Predictive Signatures of Response to Immunotherapy



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Testing B-Cell/T-Cell Signature With Response to Therapy



Published data: Van Allen, et al. "Genomic correlates of response to CTLA4 blockade in metastatic melanoma." *Science* (2015); aad0095.
 PMID: 26359337

Published data: Tanioka, et al. "Integrated Analysis of RNA and DNA from the Phase III Trial CALGB 40601 Identifies Predictors of Response to Trastuzumab-Based Neoadjuvant Chemotherapy in HER2-Positive Breast Cancer." *Clinical Cancer Research* 24.21 (2018): 5292-5304.
 PMID: 30037817

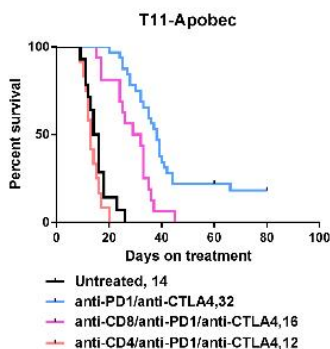
Published Data: Echavarria, et al. "Pathological response in a triple negative breast cancer cohort treated with neoadjuvant carboplatin and docetaxel according to Lehmann's refined classification." *Clinical Cancer Research* (2018); clincanres-1912.
 PMID: 29378733

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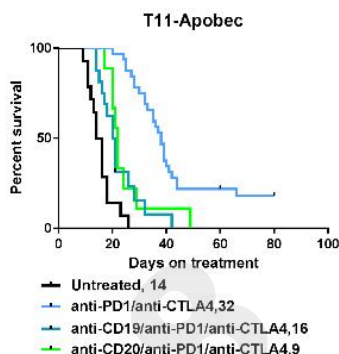


Examining the role of T Cells and B Cells in Response to Immune Checkpoint Therapy

T Cell Depletion



B Cell Depletion



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Summary

- Increasing mutation load of TNBC mouse models sensitizes tumors to immune checkpoint therapy and increases immune cell infiltration.
- We created a RNA-seq dataset of 290 mouse mammary tumors from multiple GEM Models annotated for treatment and response.
- We identified a B Cell/T Cell Co-cluster expression signature that predicts response to immune checkpoint therapy, neoadjuvant chemotherapy, and trastuzumab+paclitaxel.
- We identified a functional role for B Cells in mediating a response to immune checkpoint inhibitors in GEM Models.

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