SITC 2016

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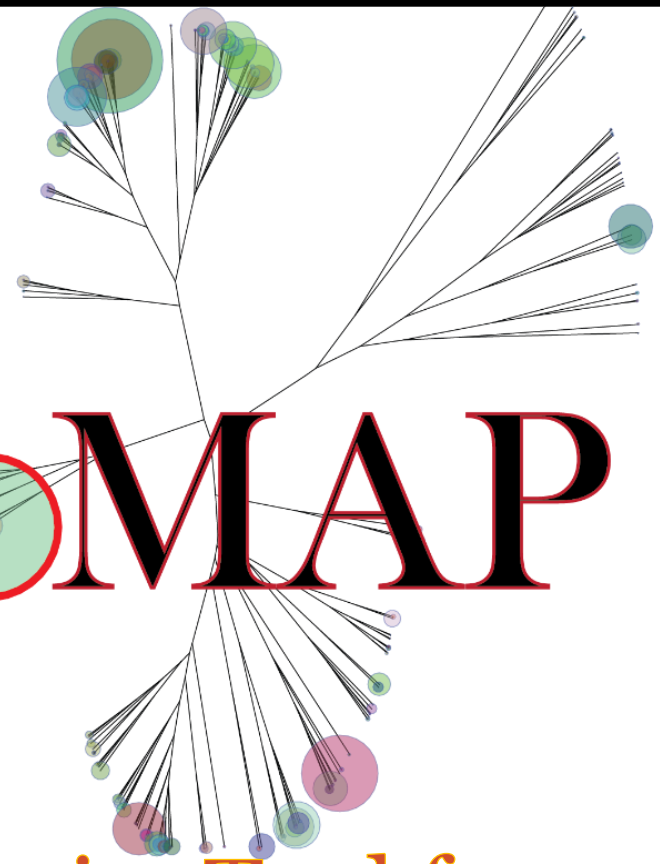
Society for Immunotherapy of Cancer



ImmunoMAP

A Novel Bioinformatics Tool for Immune Cell Repertoire Analysis

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Presenter Disclosure Information

John-William Sidhom

The following relationships exist related to this presentation:

No relationships to disclose

Overview

- Algorithm Overview
- Basic Science Application
  - Understanding Antigen-Specific Responses in Naïve and Tumor-Bearing Setting
- Clinical/Translational Application
  - Revealing signatures associated with responders on checkpoint blockade

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Background

- Advent of sequencing of T Cell Receptor CDR3
  - Understanding Immune Responses to Cancer
- BIG DATA
  - Clones
  - Frequency (Reads)
  - V,D,J usage
- Difficult to parse data into meaningful biological conclusions

Adaptive biotechnologies®

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Current Approaches

- *Diversity of Individual Repertoire*
  - Shannon Entropy – measure of diversity as a function of # of sequences & frequency[1]
- *Comparing Multiple Repertoires*
  - Tracking *exact* clonotypes (at nucleotide or amino acid level)[2,3]

Ignore Sequence Relatedness & Structure

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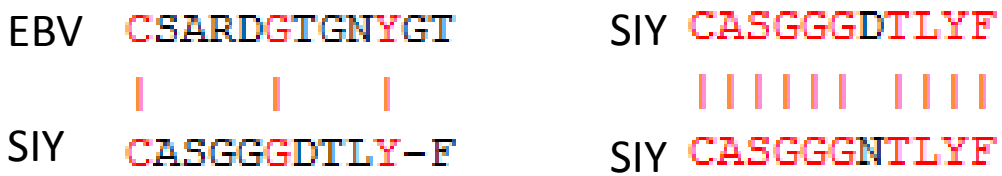
Phylogenetic Approach

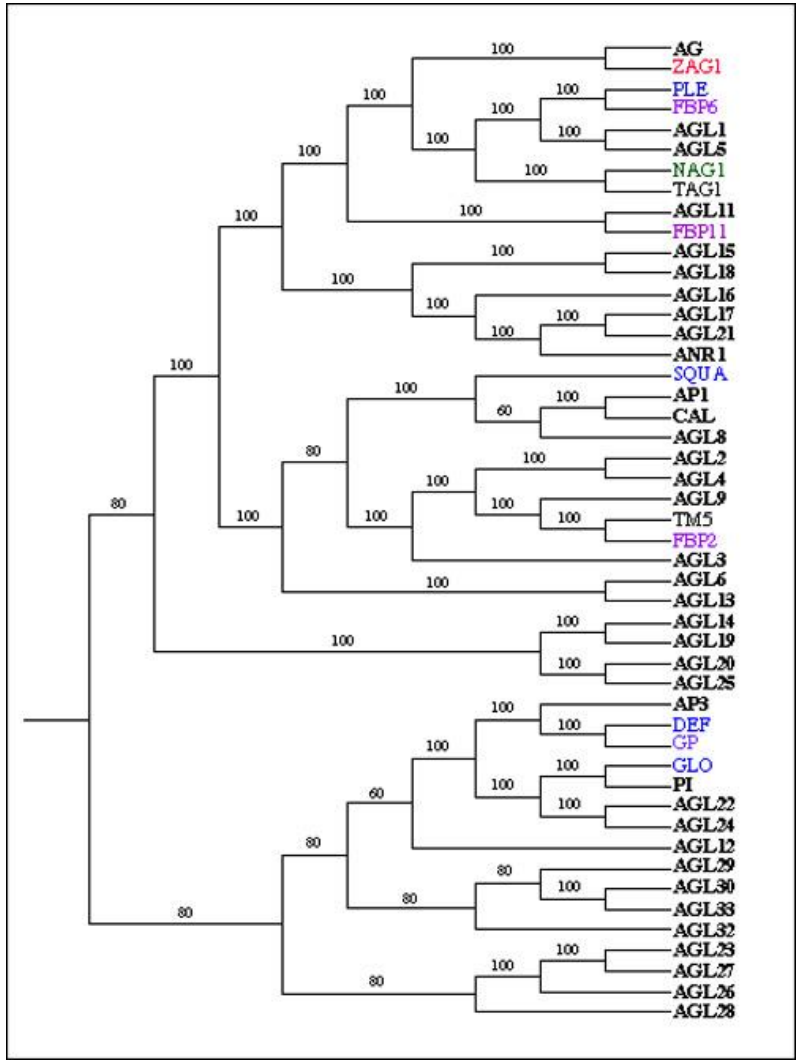
- Evolutionary Biology Approach
- Phylogenetic 'distance' can be used to understand how a collection of sequences is related to itself and other samples
  - Function of Sequence Alignment Scores



Phylogenetic Distance

0.2481

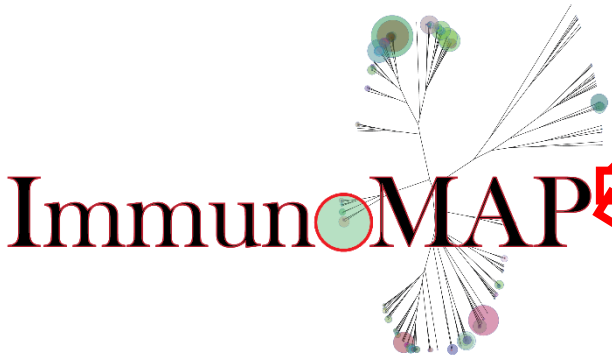
0.9884



Overview of…

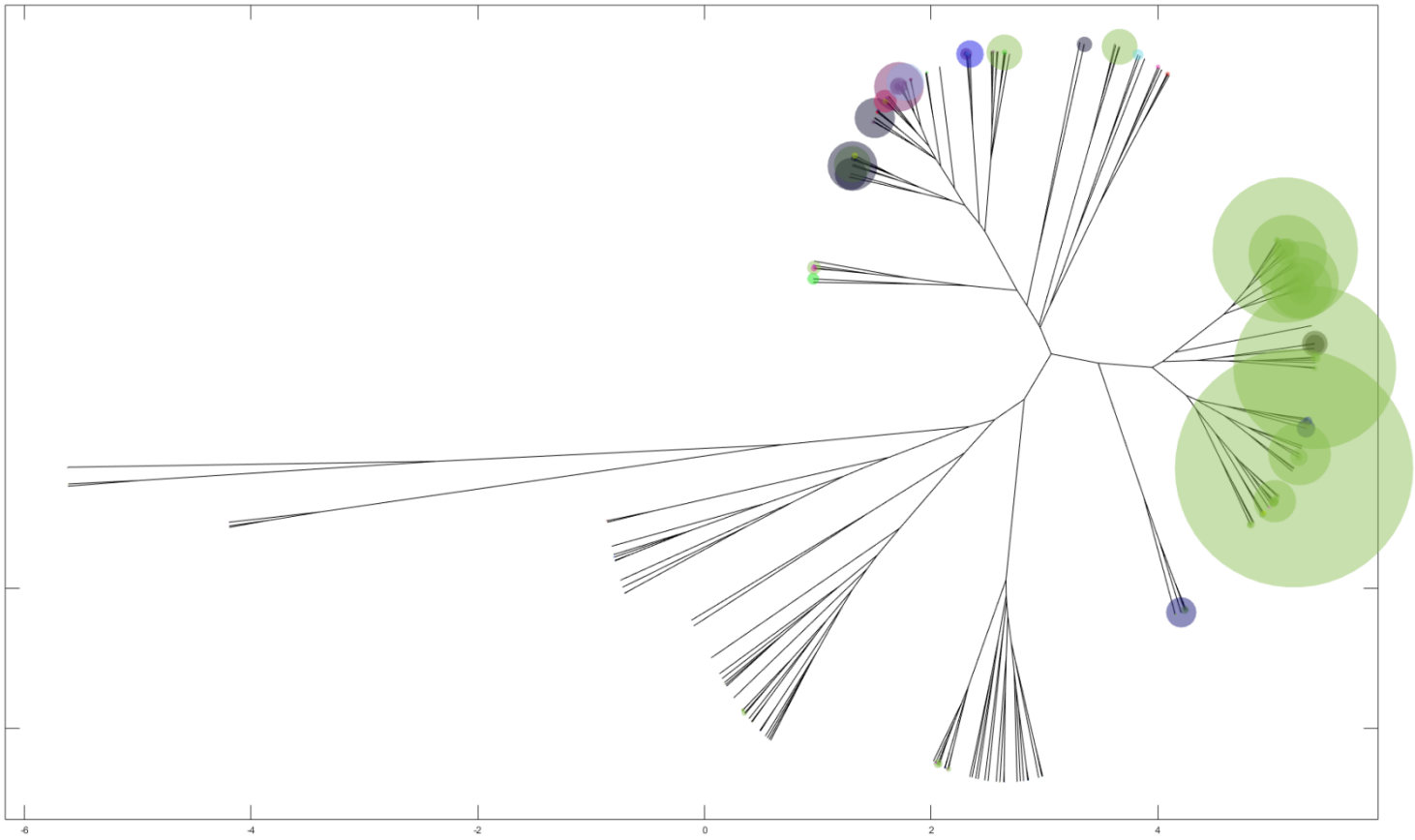
Sequencing Data
(Sequence, Frequency, VDJ Usage)

aminoAcid	count (ter	frequency	cdr3Lengt	vMaxResc	vFamilyNa	vGeneNar	vGe
CASSLPRDRSAETLYF	55	0.073788	48	TCRBV16-(	TCRBV16	TCRBV16-(	
CASSGTGGSTEVFF	35	0.048739	42	TCRBV13-(	TCRBV13	TCRBV13-(	
LCQQSGDNTGQLYF	34	0.047961	42	TCRBV26-(	TCRBV26	TCRBV26-(	
CASSQGLGGNAEQFF	33	0.044997	45	TCRBV05-(	TCRBV05	TCRBV05-(	
CASRTGAYEQYF	23	0.032259	36	TCRBV16-(	TCRBV16	TCRBV16-(	



- Weighted Phylogenetic Trees
- Dominant Motif Analysis
- TCR Diversity Score

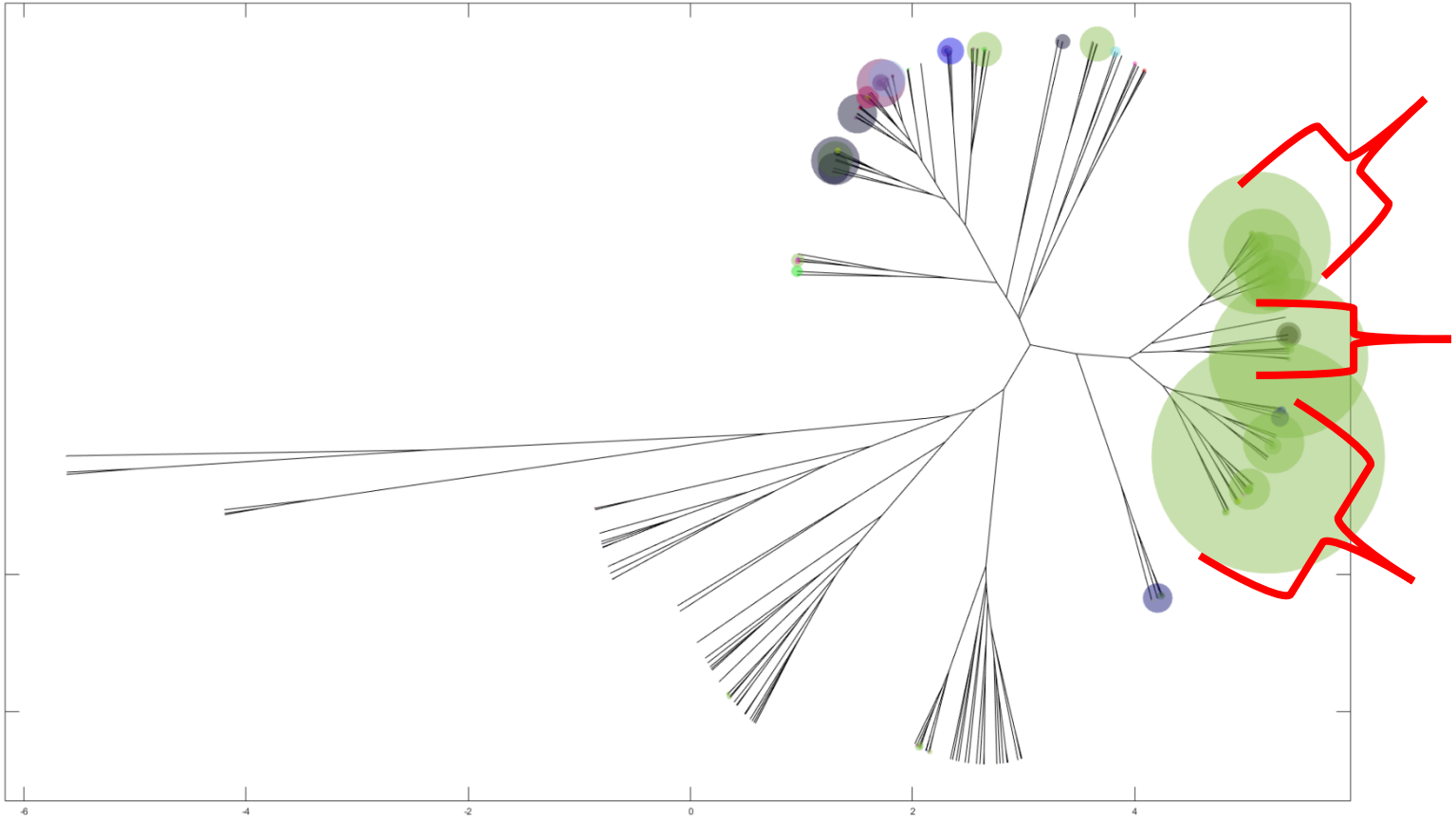
Weighted Phylogenetic Trees



Color of Circle: V-Beta Usage
Size of Circle: Frequency of Sequence

Dominant Motif Analysis

Clusters of sequences based on phylogenetic distance and frequency selected and termed, '*Dominant Motifs*'



Color of Circle: V-Beta Usage
Size of Circle: Frequency of Sequence

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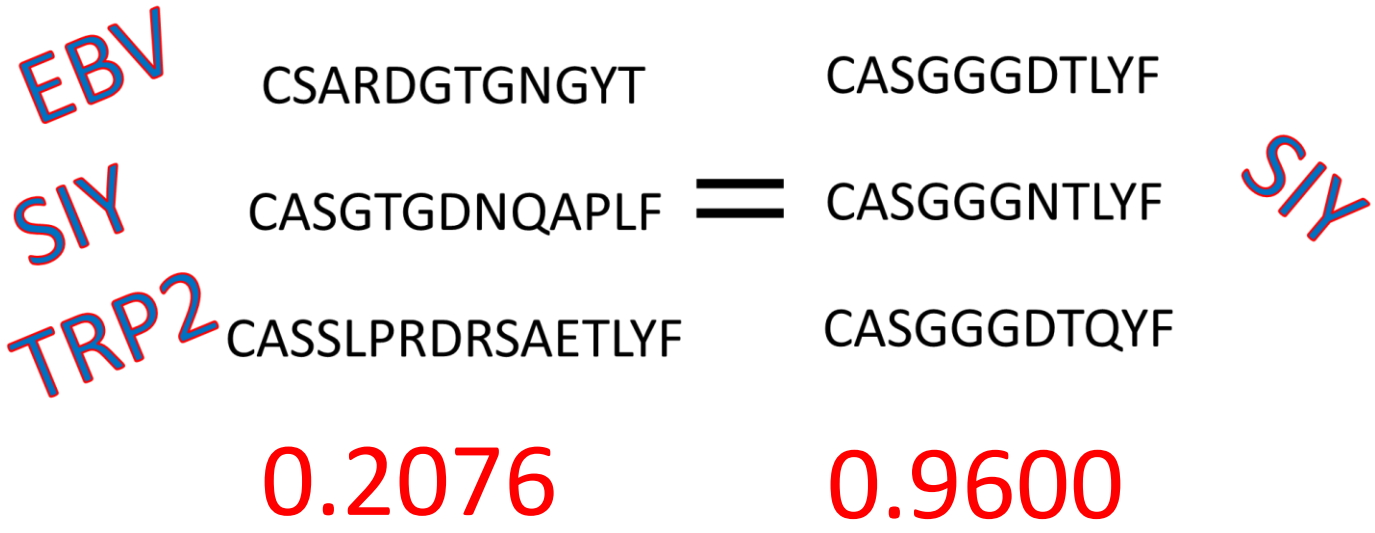
TCR Diversity Score

- Score = average phylogenetic distance of all sequences in a sample.
- Score ranges from 0 to 1
  - 1 = All Sequences Identical
  - 0 = All Sequences Infinitely Different



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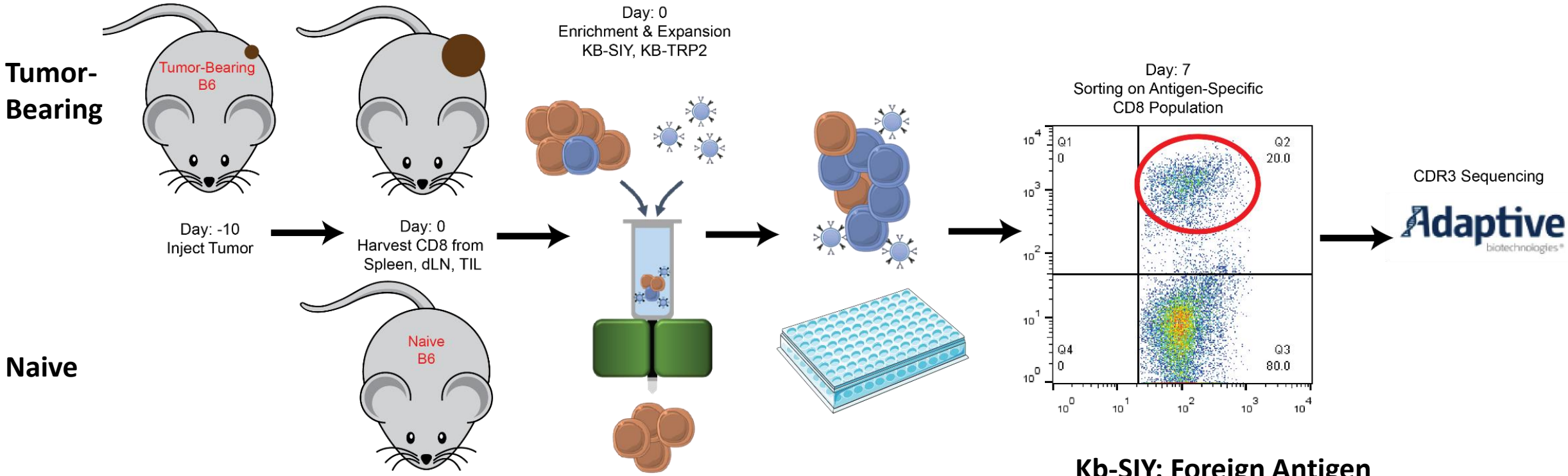
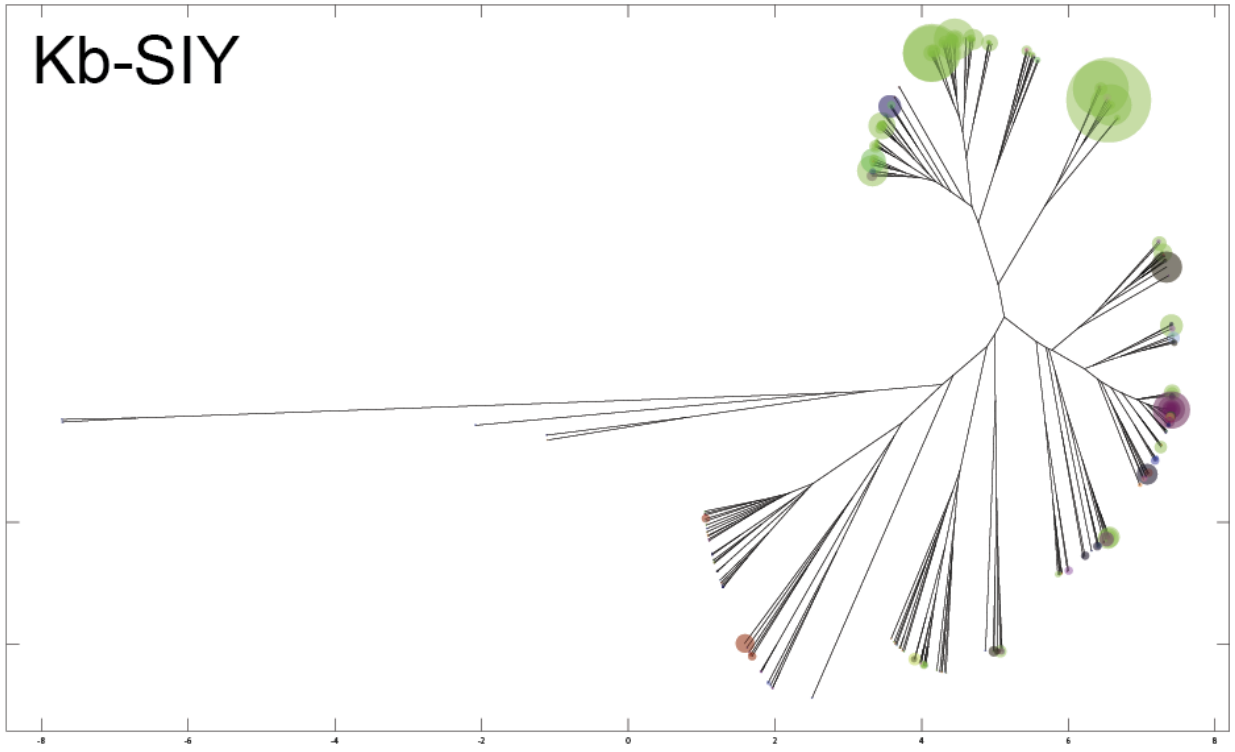
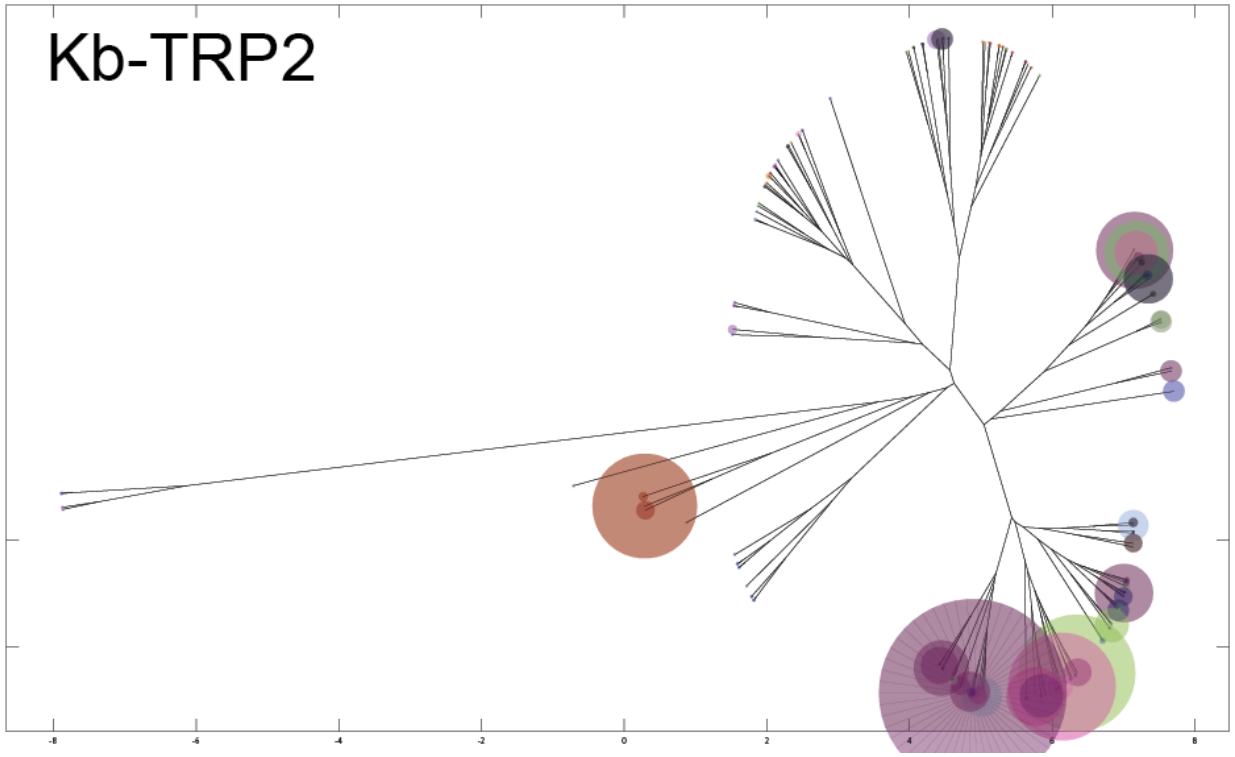
Antigen-Specific Responses in Naïve and Tumor-Bearing Settings



Kb-SIY: Foreign Antigen
Kb-TRP2: Self Antigen

Weighted Phylogenetic Trees – Naïve





Color of Circle: V-Beta Usage
Size of Circle: Frequency of Sequence

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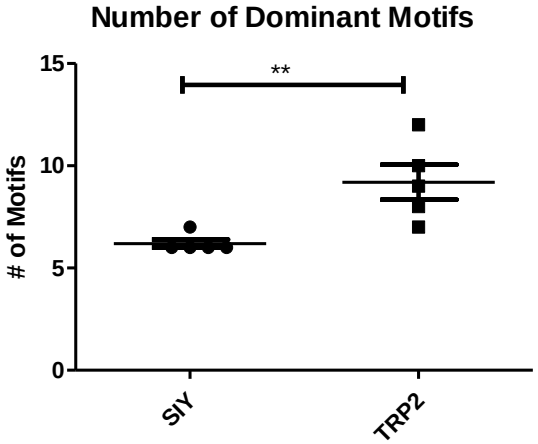
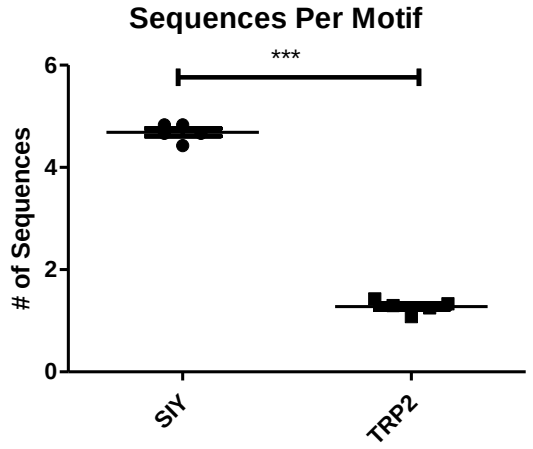
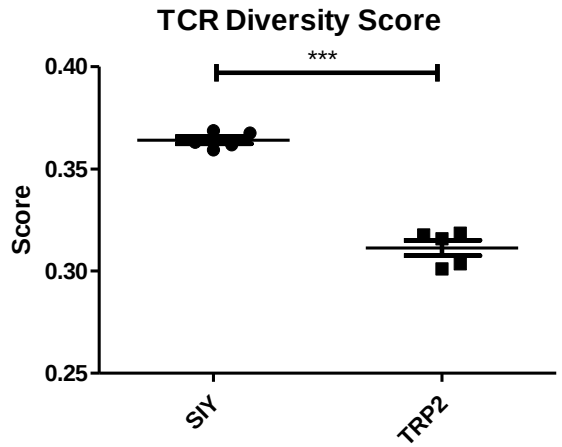
Dominant Motif Analysis – Naïve







SIY

Kb-SIY	Motif 1	Motif 2	Motif 3	Motif 4	Motif 5	Motif 6
Contribution to Response (%)	3.37	10.65	7.83	4.46	4.67	3.59
Alignment	CASGAGDYAEQFF CASGTGDYAEQFF CASGQGDYAEQFF CASSGGDYAEQFF CASGAGDLAEQFF CASGTGEGAEQFF	CASSFGGGEDTQYF CASSFGGGQDTQYF CASSFGGFQDTQYF CASSLGGGADTQYF CASSLGGGGDTQYF CASSLGGGPDTQYF CASSLGGDQDTQYF CASSLGGNQDTQYF CASSLGGGQDTQYF CASSLGGLQDTQYF CASSFGGNQDTQYF CASSWGGNQDTQYF CASSLAGNQDTQYF CASSLAGNQGTQYF CASSRGGGLDTQYF CASSLQGVQDTQYF CASSLRGPQDTQYF CASSPRGFQDTQYF CASSRQGPQDTQYF CASSSKGPQDTQYF CASSREGNQDTQYF CASSRKGNQDTQYF	CASGGGDTLYF CASGGGNTLYF CASGGGDTQYF CASGTGDTQYF CATGTGDTQYF CASGTGDTLYF CASGDGGTQYF CASGDPDTQYF	CASGGLGEQYF CASGGLGGQYF CASGGLGVQYF CASGGQGDQYF CASGGQGEQYF	CASATGDNQAPLF CASGTGDNQAPLF CASGTGDNRAPLF	CASSDAYSNQAPLF CASSDSYNNQAPLF

TRP2

Kb-TRP2	Motif 1	Motif 2	Motif 3	Motif 4	Motif 5	Motif 6
Contribution to Response (%)	10.68	5.66	5.50	3.07	5.66	6.15
Sequences	CASSLPRDGSAETLYF CASSLPRDRSAETLYF CASSLPSGSSAETLYF CASSRSRDNSAETLYF	CASSLRGFEQYF CASSPRGREQYF	LCQQSGDNTGQLYF	CASSQEGTGGREQYF	CASSQGLGGNAEQFF	CASSGTGGSTEVFF
	Motif 7	Motif 8				
Contribution to Response (%)	3.07	4.05				
Sequences	CASSLDSGGSQDTQYF	CASRTGAYEQYF				

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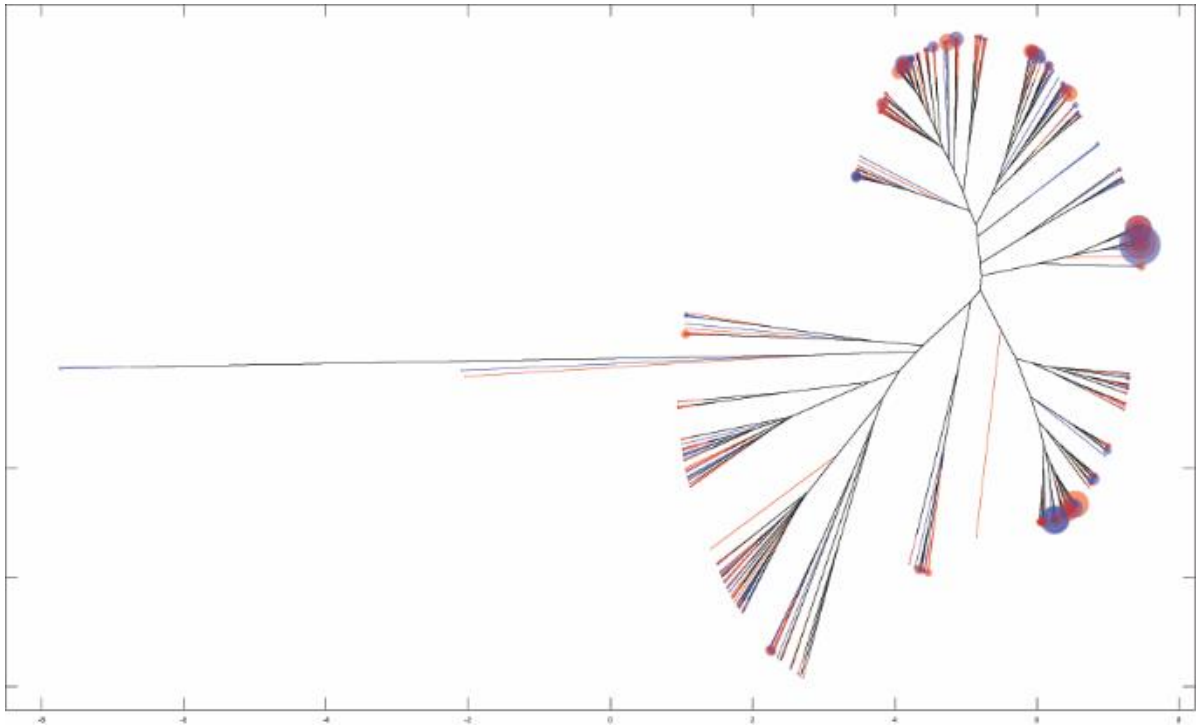
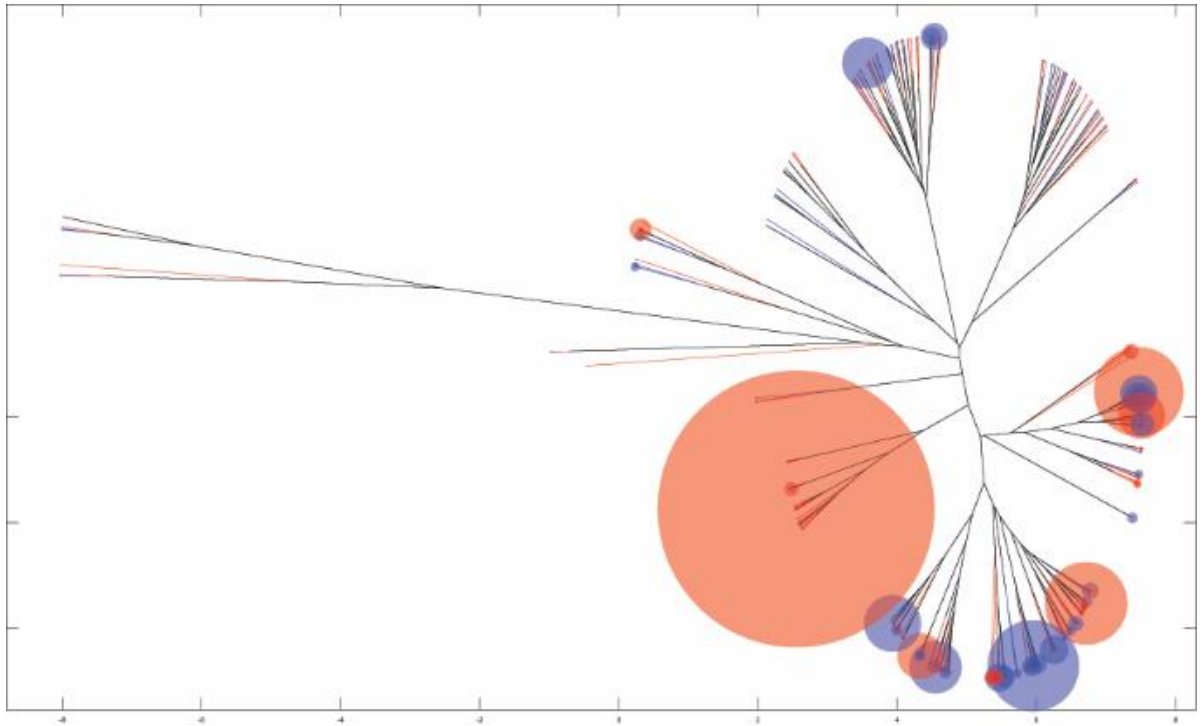
Weighted Phylogenetic Trees – Tumor-Bearing

SIY



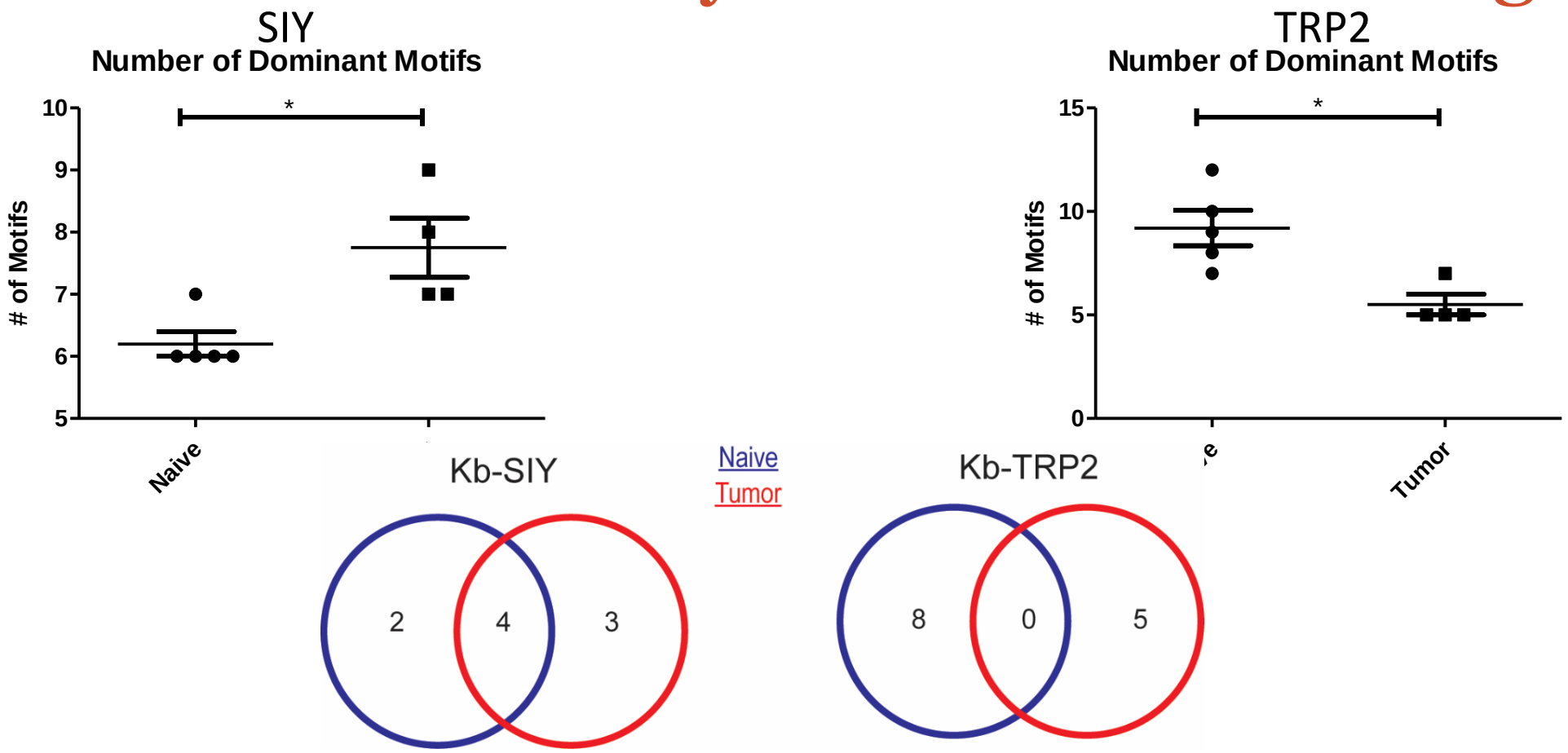
TRP2



Blue: Naïve Response

Red: Tumor-Bearing Response

Dominant Motif Analysis – Tumor-Bearing



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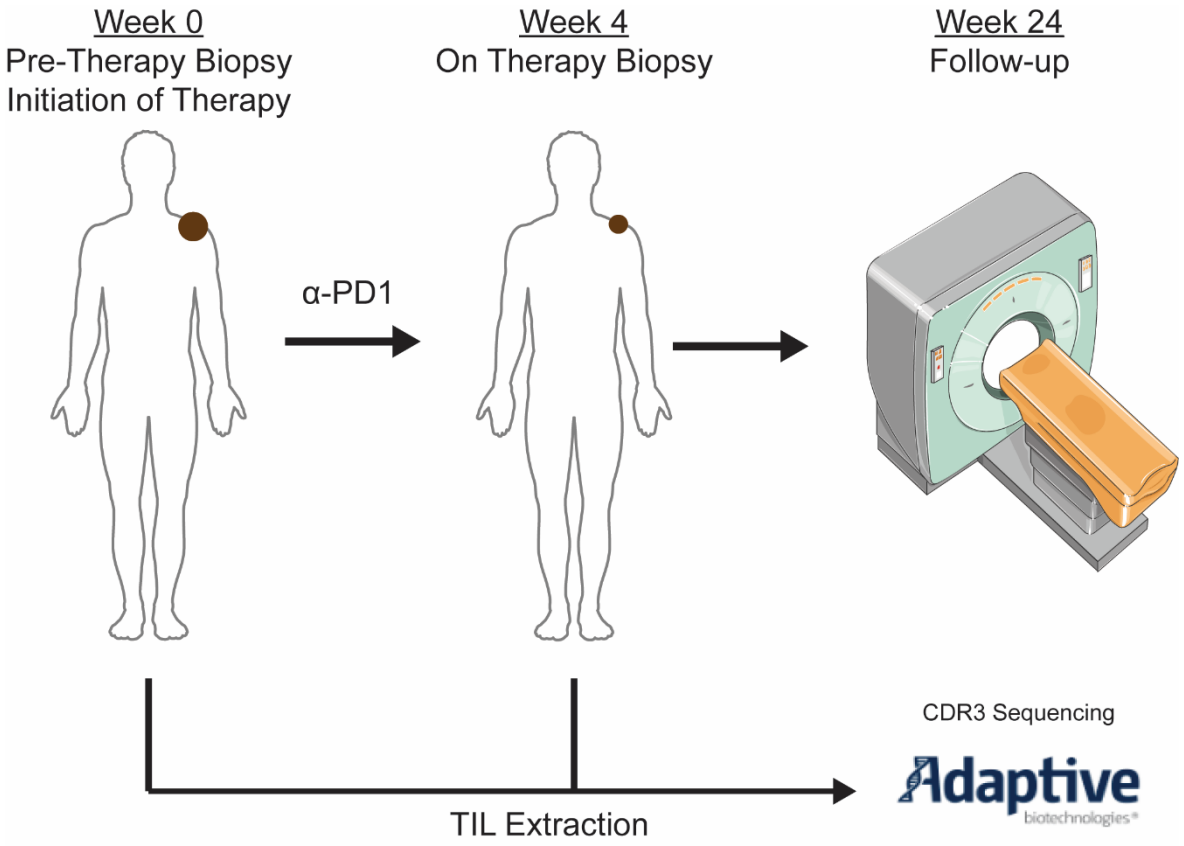
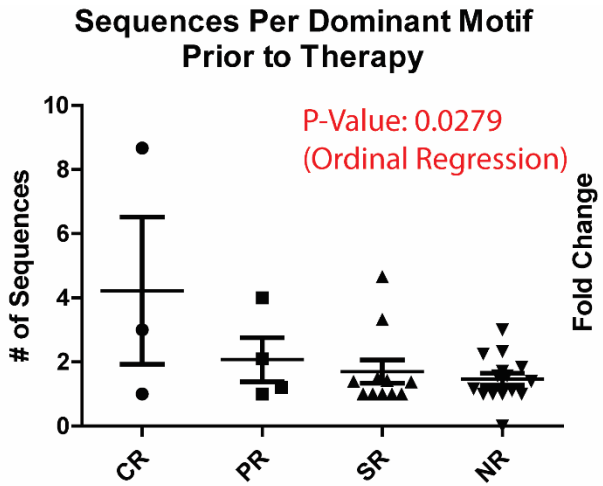
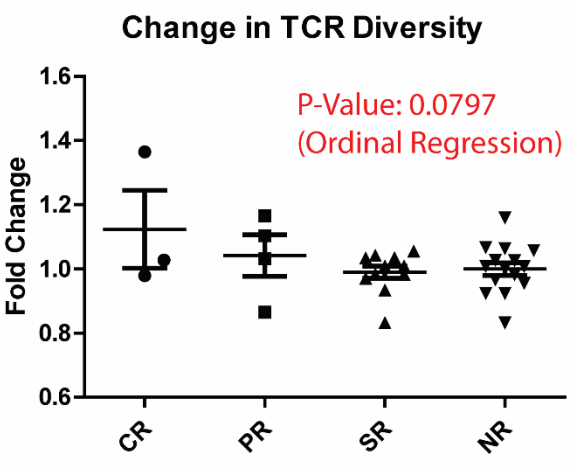
Analysis of Tumor-Infiltrating Lymphocytes from Melanoma Pts. Undergoing α-PD1







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Concluding Points

- Current approaches to TCR Repertoire Analysis do not address structural/sequence aspects of the response
- ImmunoMAP uses a novel phylogenetic approach to understand repertoire structure and diversity
- Insights from ImmunoMAP to:
  - Understand the basic biology of immune responses across many scientific and medical fields (oncology, autoimmunity, infectious disease)
    - Differential immune pressure on various tumor antigens
  - Characterize responses of patients who respond/resist immune therapies

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References

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