

Pre-transplant TCR Network Topology Predicts Kidney Allograft Rejection

Nick Borchering, MD, PhD

Department of Pathology and Immunology, WUSTL

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Disclosures

Worked

- Santa Ana Bio
- Omniscope

Consulted

- Epana Bio
- Starling Bio
- Columbus Instruments

Stock

- Epana Bio

Sold Software

- Columbus Instruments

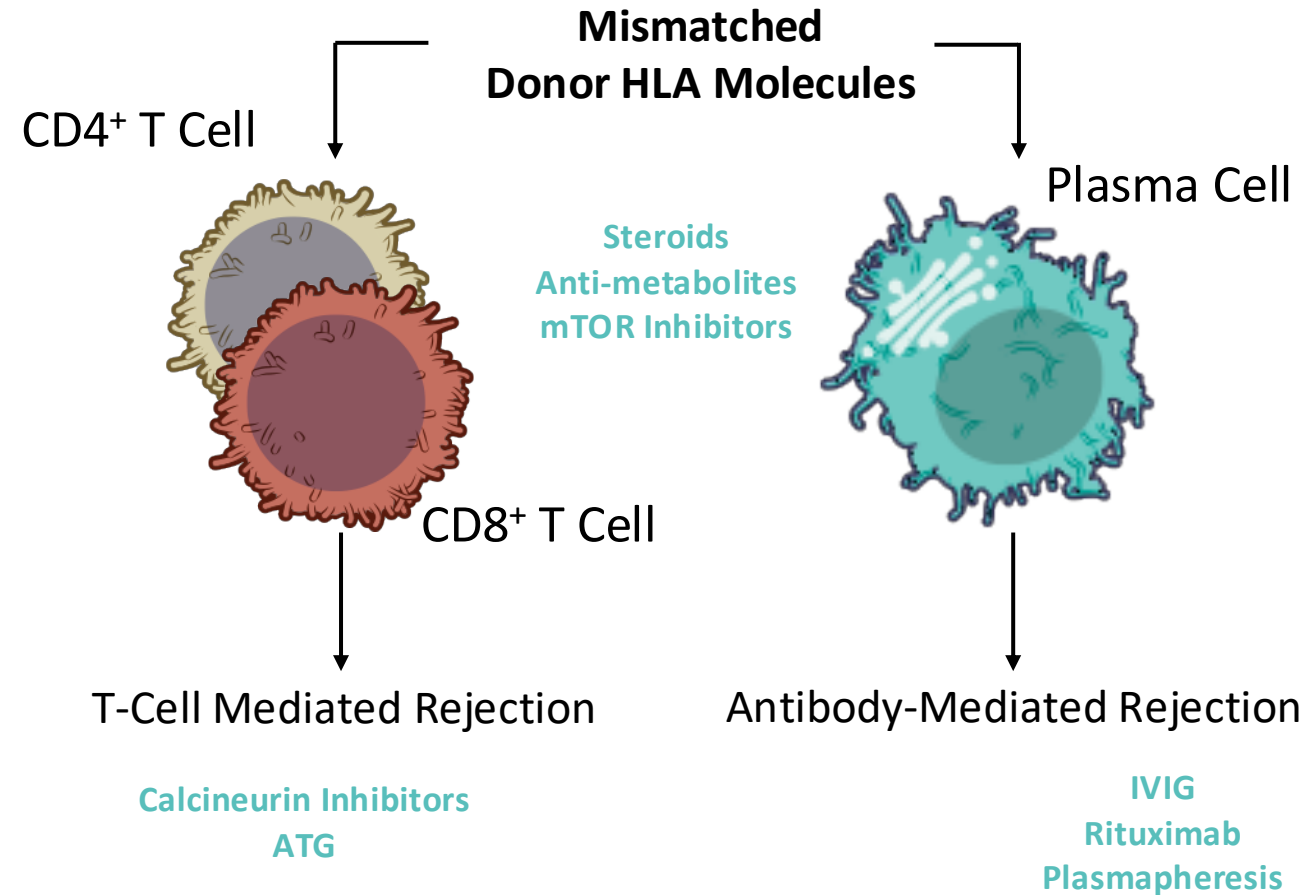
None related to the topics in this presentation

Solid Organ Transplantation

Definitive modality for care in end-stage organ failure (kidney, liver, heart, lung, pancreas).

Cost of Immunosuppression **\$2-2.5 Billion**

Incidence	Globally	150,000
	United States	50,000 (65% kidney)
	WashU	350 Renal 50 Liver 50 Lung

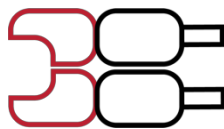


What Does "Matching" Mean?

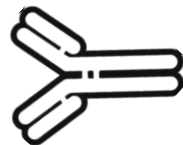
ABO compatibility



HLA typing

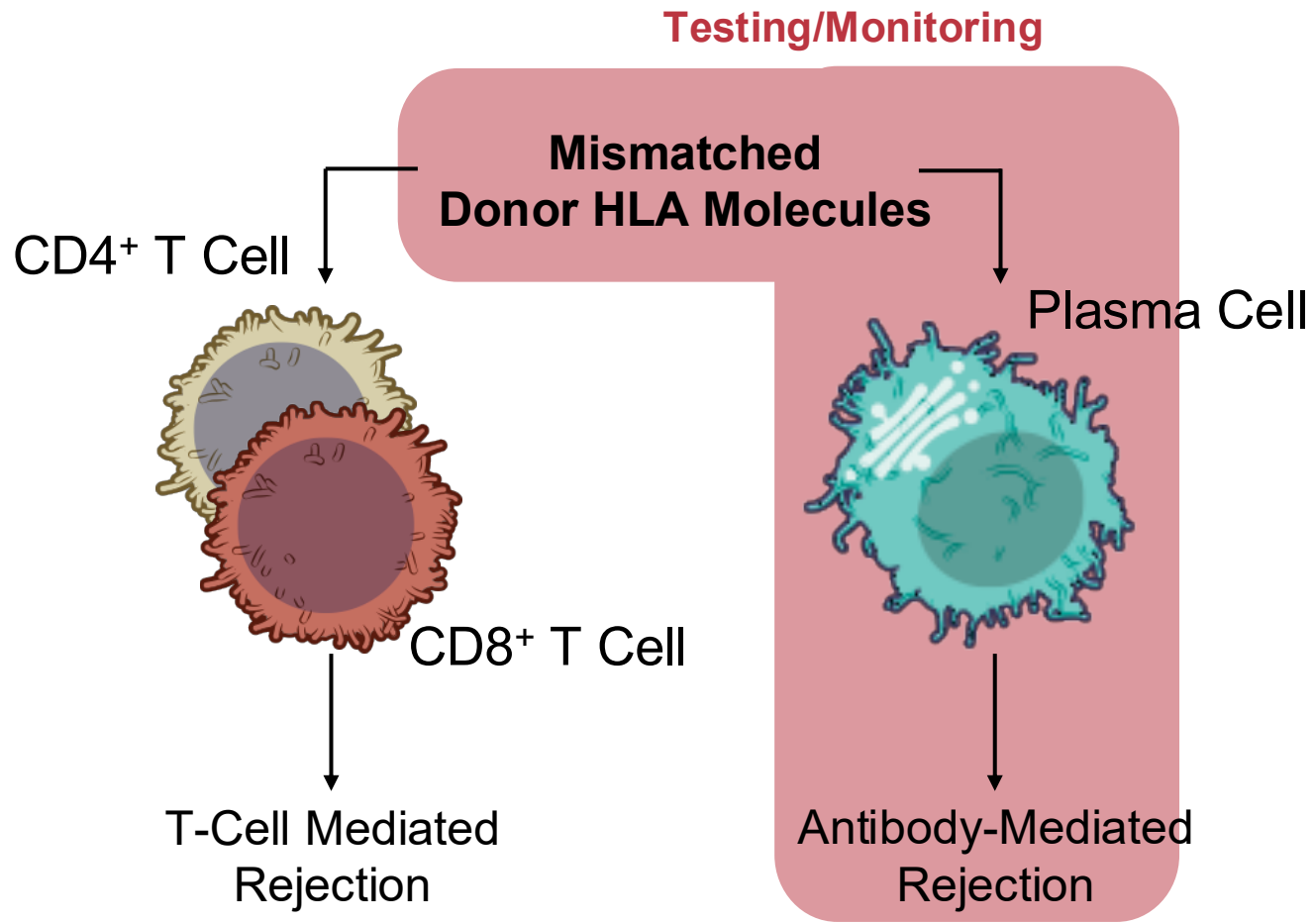


Serological Reactivity



Pretransplant Risk Stratification

The Clinical Blind Spot



10-15%

ACUTE REJECTION RATE

Rejection occurs in year one despite rigorous HLA matching.

0

ROUTINE T-CELL SCREENING

Routine pre-transplant T cell assessment in current practice

TCR Primer: Measuring the Immune Army

What are TCRs?

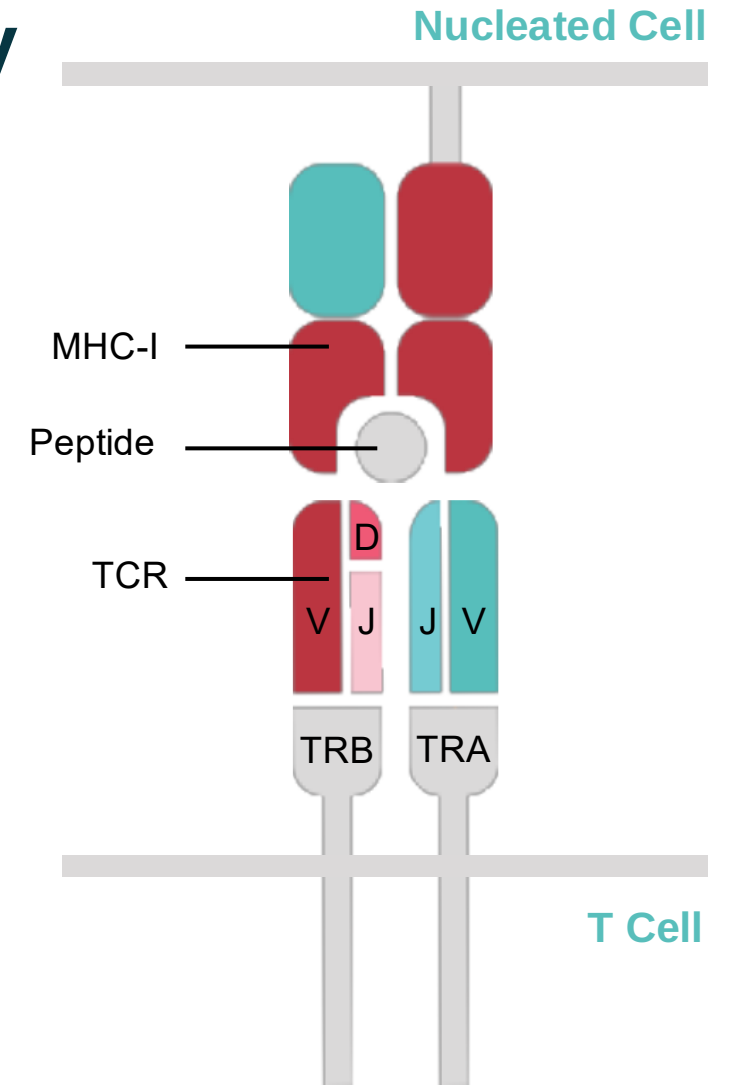
T-Cell Receptors (TCRs) are molecular keys on the surface of T-cells that recognize specific "targets" or antigens.

The Repertoire

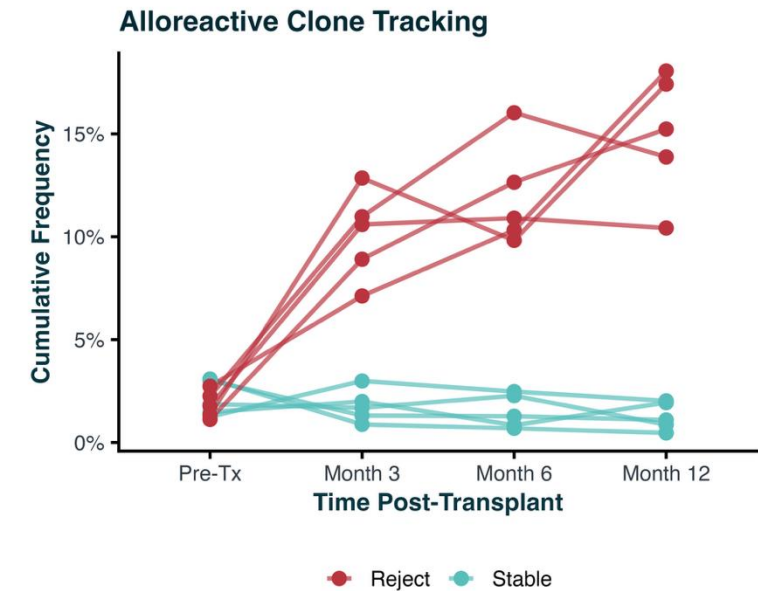
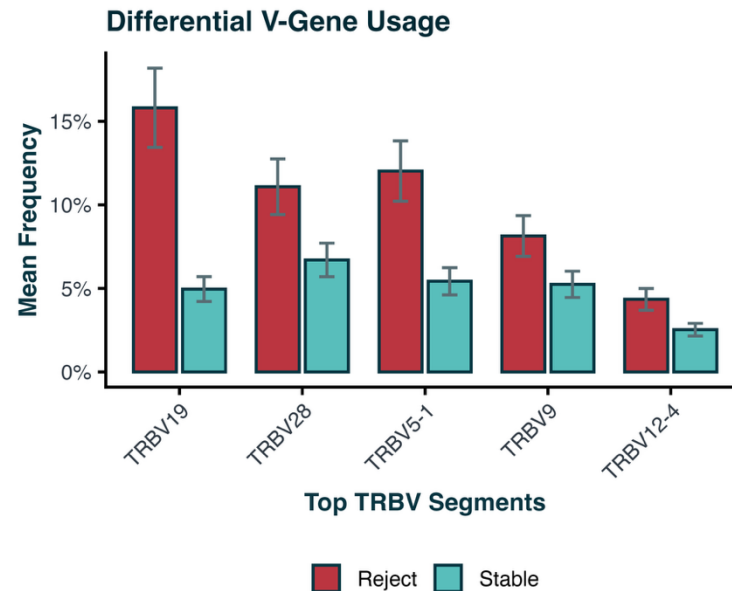
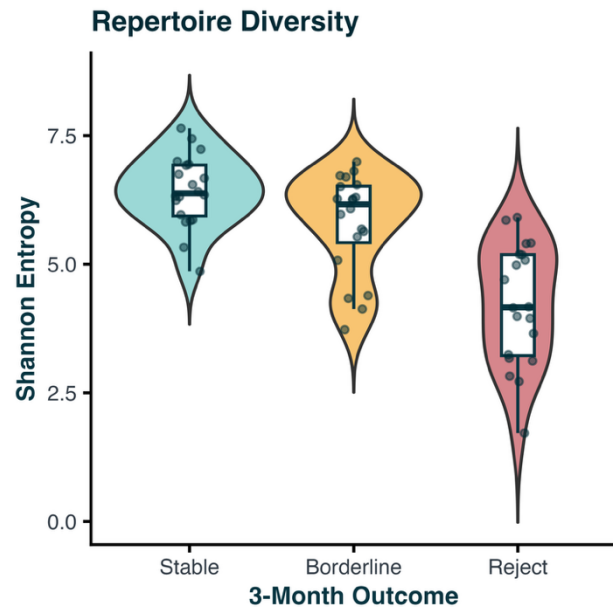
A "repertoire" is the massive collection of diverse T-cells in a patient. We can sequence these to get a fingerprint of the immune state.

Hypothesis

TCR repertoire architecture encodes functional risk of solid organ rejection.



Why Current Approaches Struggle



Measures

Total repertoire variety (clonality)

Frequency of gene segment usage

Individual alloreactive clones

Limitations

Compresses complex data into one number; ignores relationships.

Coarse signal; often vanishes post-transplant.

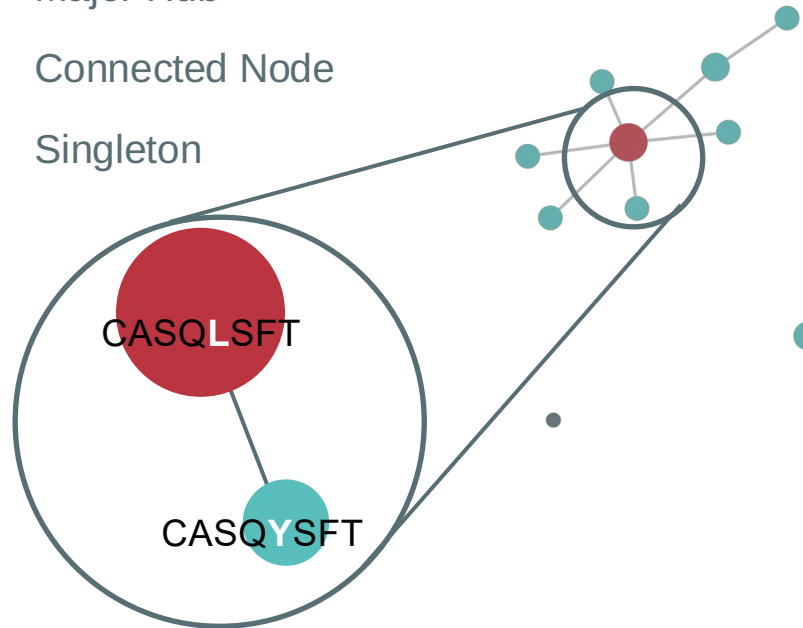
Requires multi-day culture; not scalable for pre-op clinics.

Repertoires as Social Networks

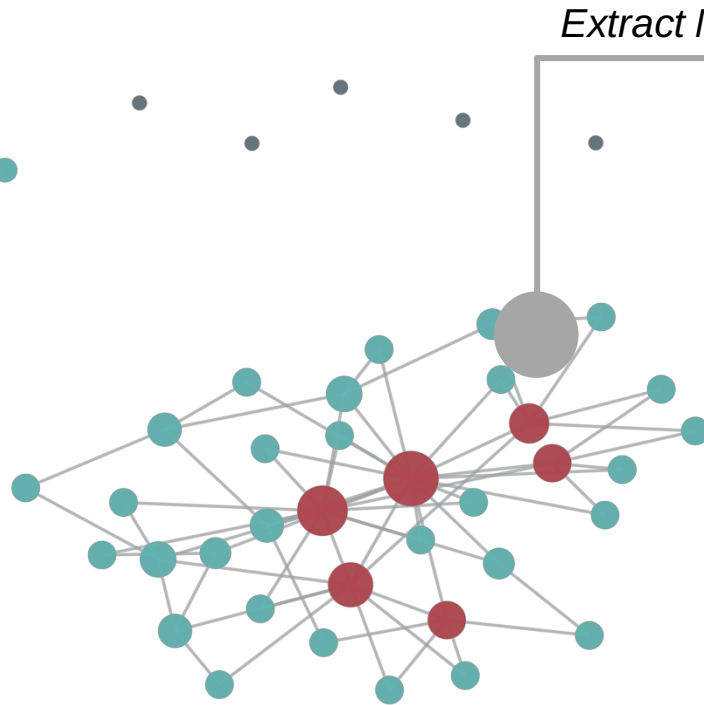
Nodes = Clone (TCR Amino Acid sequences).

Edges = Sequence similarity.

- Major Hub
- Connected Node
- Singleton



Sequence Distance = 1



Degree = How many edges to a node

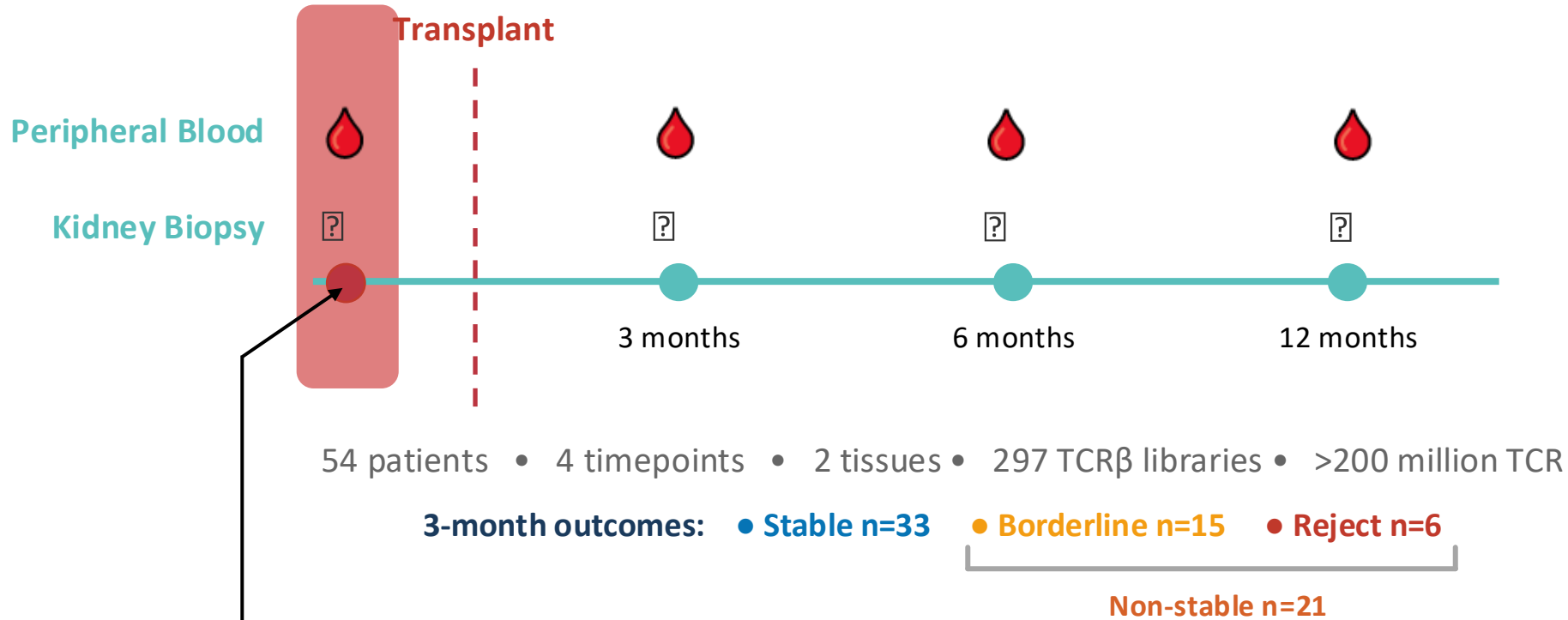
Strength = Sum of weights of all edges

Modularity = How easily a network can be divided into clusters

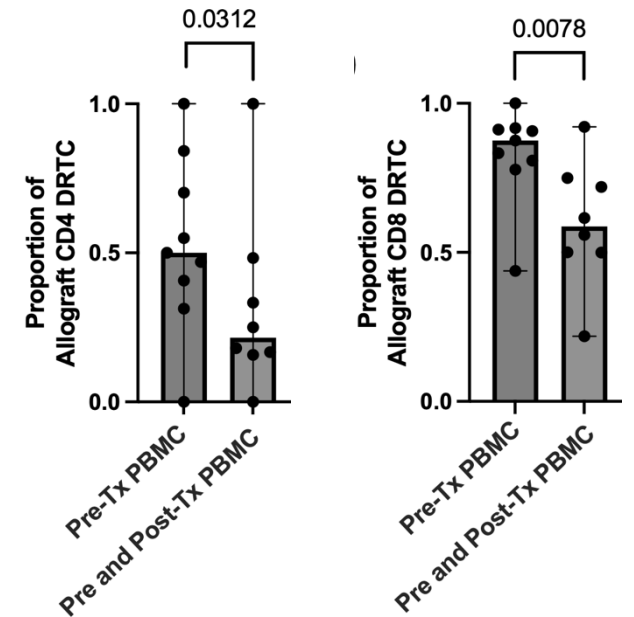
Degree Entropy = How random are the degrees across the network

Number of Metrics = 30

Architectural Integrity Requires Data Foundation



Majority of Alloreactive T Cells are in the Blood Before Transplant

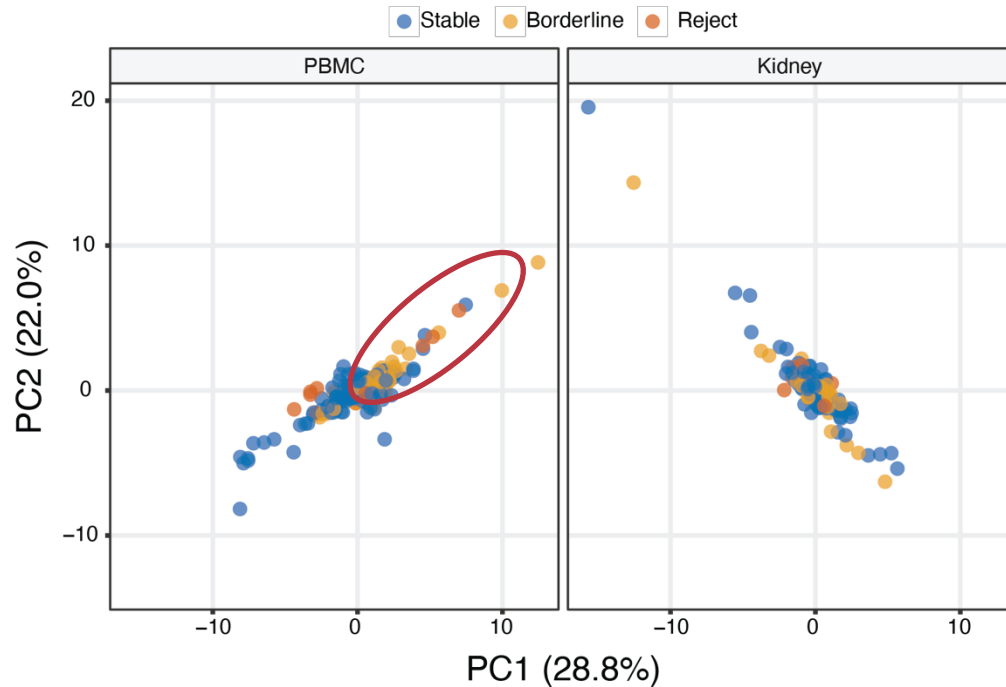


CD4+ and CD8+
Mixed Lymphoid Reaction

Do network topology metrics of the **pretransplant** immune repertoire significantly differentiate **stable versus unstable** graft outcomes?

Graft Outcomes Leave a Topological Fingerprint

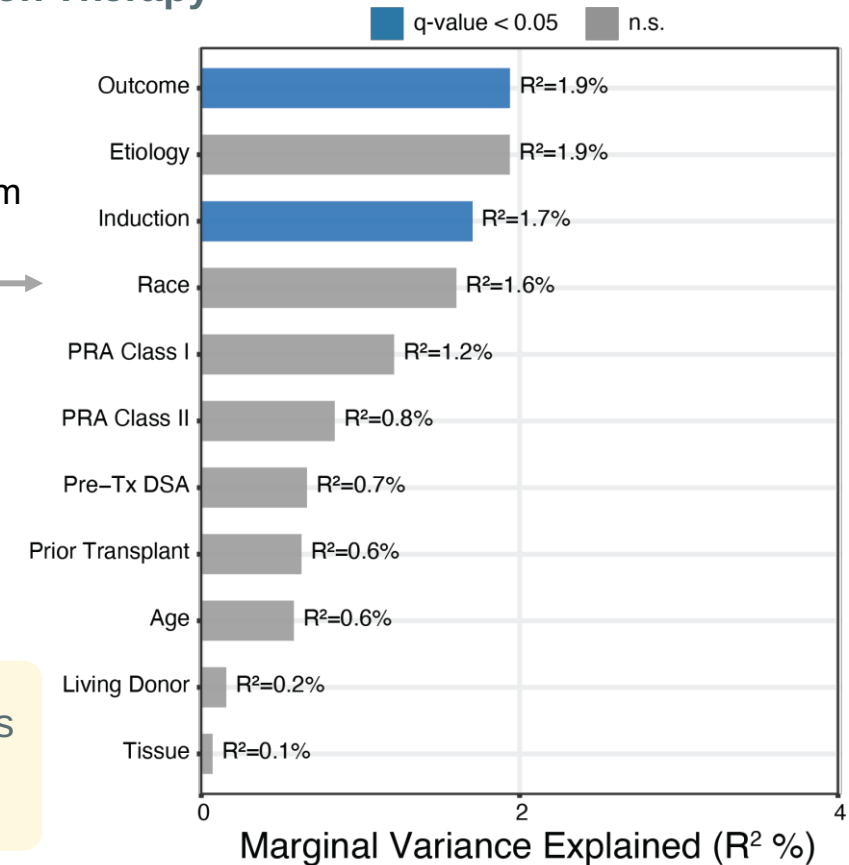
Pretransplant Samples



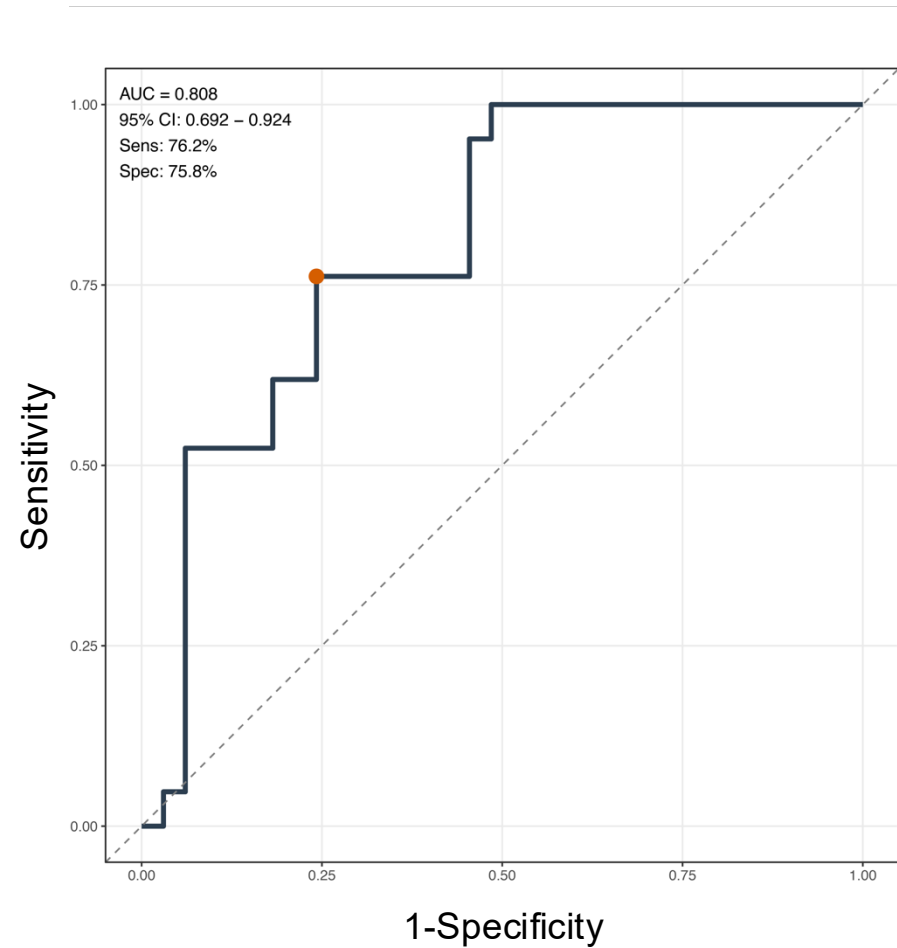
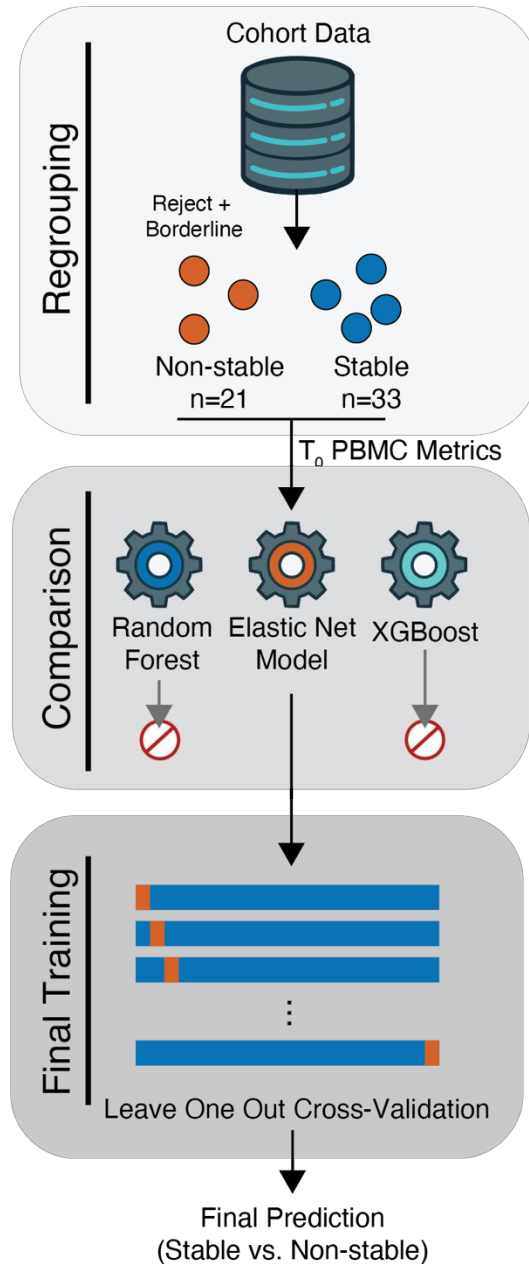
Non-stable patients have **higher PC1** = more fragmented, less connected networks

Signal Location: Found in PBMC (blood), not kidney tissue

Network Topology of TCR associated with **Graft Outcome** and **Induction Therapy**



Pretransplant Acute Rejection Prediction Model



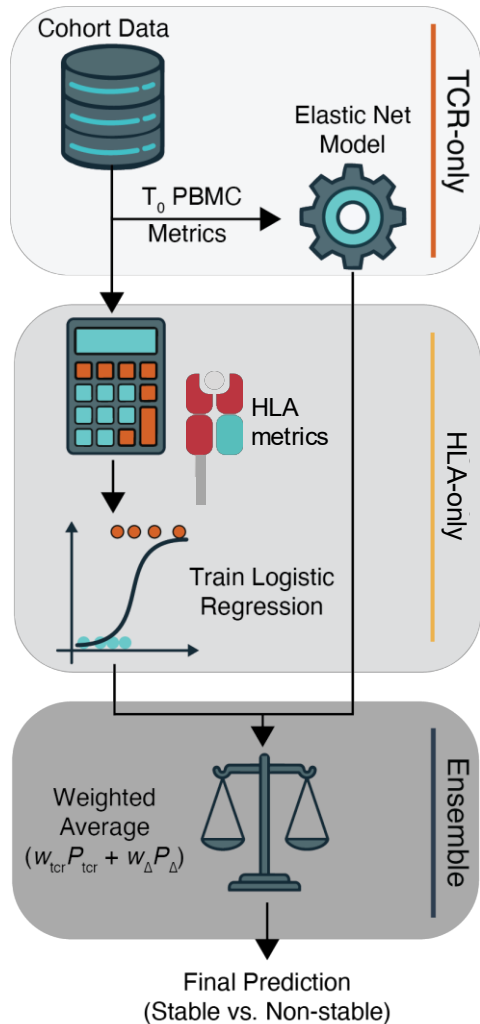
0.81
PRE-TRANSPLANT AUC

Degree Entropy
Mean Degree
Mean K-Core
Mean Strength

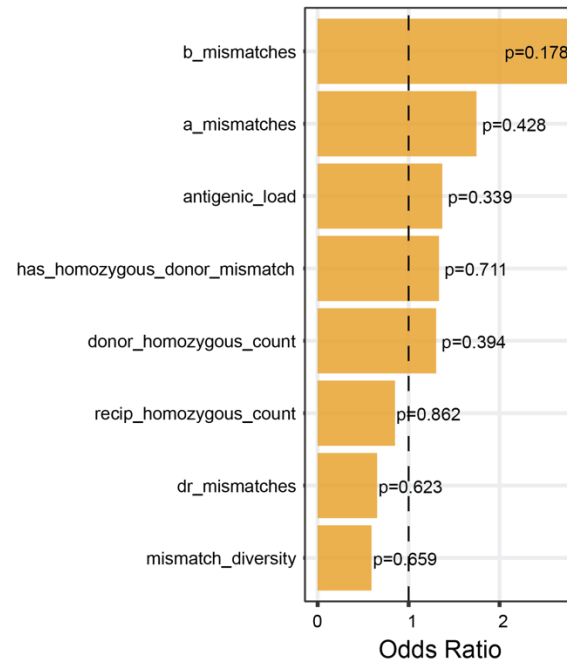
All Major
Components
of PC1

Events per variable (EPV) to limit overfitting

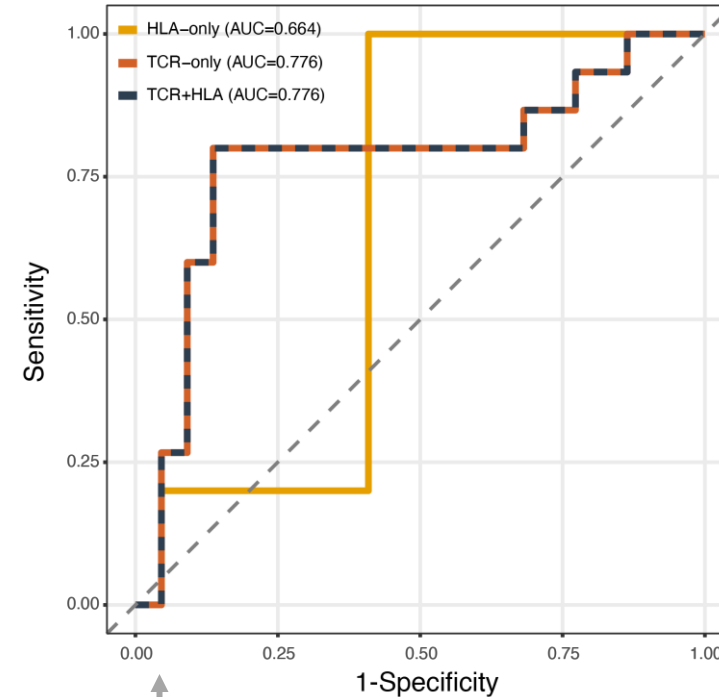
TCR Predictive Signal is Orthogonal to HLA Matching



No HLA Variable
Predicted Graft Outcome



Ensemble Model Set HLA-only
Model to W = 0



Major Caveat: HLA Typing information available for **37 of 54** patients

Three takeaways.

1

Network topology is a tractable, pre-operative readout.

A single blood draw, bulk TCR β sequencing, no donor cells, no culture \rightarrow AUC 0.81.

2

The signal is orthogonal to HLA.

It captures functional immune readiness, not donor–recipient genetic distance \rightarrow addresses a **clinical blind spot**.

3

Further Validation is needed

Single-center cohort, n = 54. External multi-center validation is the first required next step.

Binary outcome only. 6 rejection events forced collapse with borderline; a three-class model would be clinically more useful.

Cross-induction generalization is limited. Understand the biases associated with immunosuppression.

No phenotypic annotation per clone. Bulk TCR β doesn't tell us if a network hub is memory, naive, regulatory, or effector.

Our Future Directions

Co-authors

Jes Sanders (Northwestern)
Greg Martens (WUSTL)
Naoka Murakami (WUSTL)
Natnael Doilicho (WUSTL)
Barbara Banbury (Adaptive)
Jie He(Northwestern)
Joseph Leventhal (Northwestern)
James Mathew(Northwestern)

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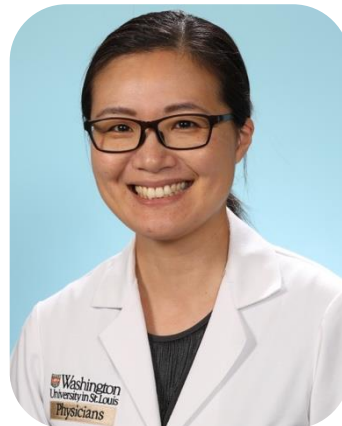
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Greg Martens



Naoka Murakami



Questions?

Link for Preprint



Link for Code



Email: borcherding.n@wustl.edu