Personalizing Kidney Transplantation:

Role and Impact of Eplet Matching

UNMC

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Overview

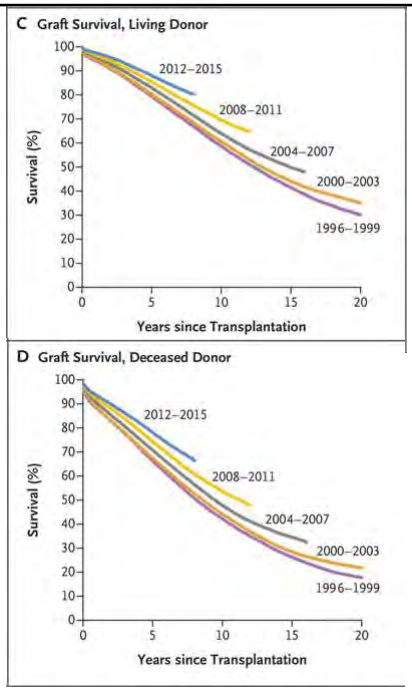
- Limitations of immunosuppression and current immunosuppression protocols
- Need for individualized immune risk stratification
- Immune risk stratification and role of HLA matching at a molecular level –HLA eplets
- Future directions

2

Short term kidney transplant and patient survival is excellent with immunosuppressive regimens resulting in progressively lower biopsy proven acute rejection (BPAR) rates (5-15%)

Long term graft survival remains suboptimal

- Half life 11-15 years
- 10 year graft loss rates with very modest improvement



S Hariharan et al NEJM 2021; 385:729-43

3

Major limits to long term transplant outcomes

- Immunologic risk is inherent to kidney transplant and alloimmune injury is a cardinal cause of graft loss
- Unwanted side effects of immunosuppression
  - Increased risk of infections and cancer
  - Off target effects of immunosuppressive medications
    - Nephrotoxicity
    - Adverse effects on blood pressure, lipids, and glucose metabolism

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The Myth of Goldilocks Immune Suppression

"Prograf target 5 to 8"

"Full dose myfortic"

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Complicated Reality

- Suppressing the immune system increases the risk of infections, cancers and side effects of immunosuppressive medications
  - The only way to completely mitigate that risk is no immune suppression

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One size fits all?

Majority of U.S. transplant center protocols use homogenous immunosuppression regimens:

- Induction immunosuppression
  - Typically rabbit ATG

- Maintenance immunosuppression
  - -Tacrolimus – higher levels initially – then taper to lower target
  - -Anti-proliferative (e.g mycophenolate)
  - -+/- steroids

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How we currently assess risk and adjust immunosuppression

Panel of Reactive Antibodies (PRA)

- High PRA is bad. Low PRA is good

HLA Mismatch

Donor Specific HLA antibodies pre and post transplant

Bad things happening to the kidney

- Rejection, graft dysfunction

Bad things happening to the patient

- Infection, cancer, medication side effects

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Protocol Driven - Reactive Immunosuppression

- Current approach results in excellent population based short term outcomes
- Subsets of patients with significant complications
  - Significant or persistent rejection
  - Adverse effects from suppressed immune system – infections/cancer
  - Side effects from medications
- Long term outcomes remain suboptimal

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Need for individualized risk stratification

- Ideal immunosuppression regimen:
  - Give as little immunosuppression as possible
  - Minimize off-target effects of immunosuppression
  - Not compromise protection from alloimmune response
- Transplant population is heterogenous with varying risk of rejection
  - Age of recipient
  - Immune memory
  - Histocompatibility with donor

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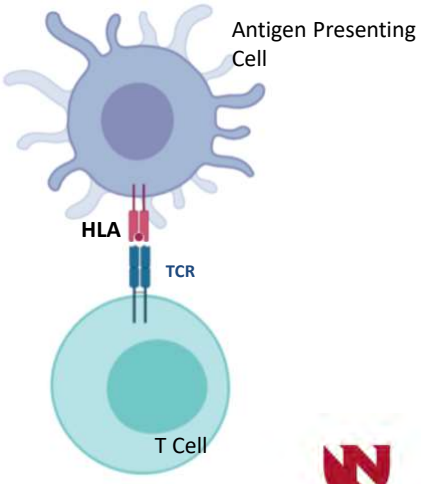
HLA Compatibility

- HLA match and mismatch
  - Match: HLA antigens shared by donor and recipient
  - Mismatch: HLA antigens in donor NOT present in recipient
- Presence (or absence) of Donor Specific Antibodies
  - Recipient HLA antibodies to donor HLA antigens



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Donor and Recipient HLA Matching HLA matching

Donor and Recipient typed for HLA genes

– Example

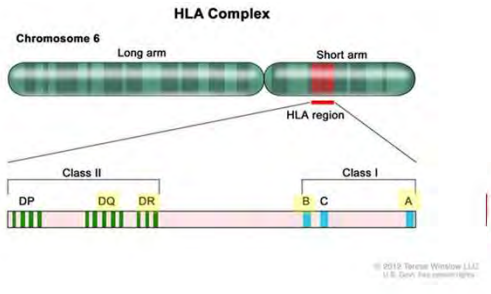
Recipient HLA type: A1 A24 B8 B35 DR15 DR 17 DQ2 DQ6

Donor HLA type: A3 A24 B8 B44 DR13 DR 17 DQ2 DQ6

3 out of 8 Antigen mismatch

HLA mismatch 1/1/1/0

1 HLA A MM
1 HLA B MM
1 HLA DR MM
0 HLA DQ MM



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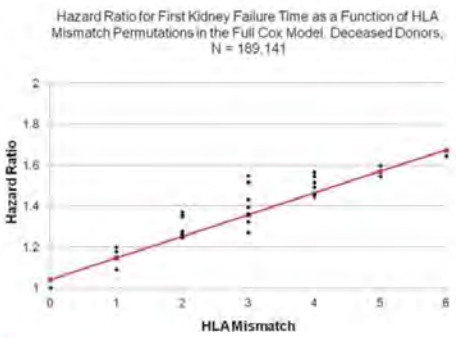
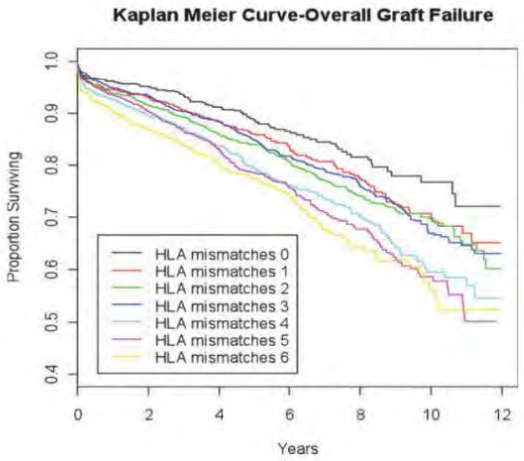
HLA mismatch

Generally greater mismatched antigens leads to increased risk for rejection and graft loss



Williams et al Transplant 2016 100(5)



Lim et at Clin Trans 2012: 26: E428-37

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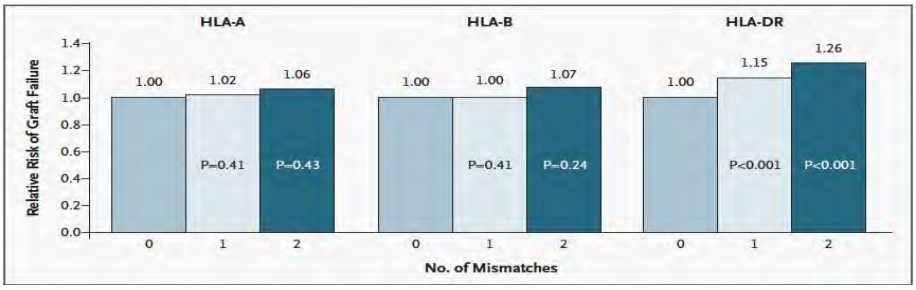
Class II HLA mismatch at DR (and DQ) associated with increased rejection and worse graft survival

Roberts et al., NEJM (2004) 350:545-51



HLA DR matching for deceased donor allocation

- Prospective recipients for a deceased donor kidney get 0 to 2 points for DR matching
  - 0 DR mismatch = 2 points
  - 1 DR mismatch = 1 point
  - 2 DR mismatch = 0 points

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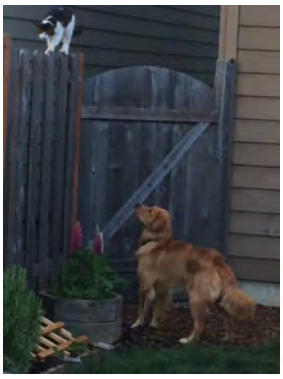
Not all HLA mismatches are equal

Donor HLA antigens may have varying ability to generate an alloimmune response in a specific kidney transplant recipient

Variable alloimmune response dependent upon degree of difference between donor and recipient antigens (and ability of recipient to react to donor HLA)



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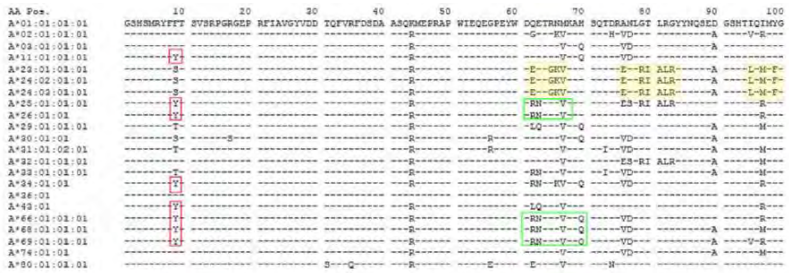
HLA protein sequences are both conserved (required for function) and polymorphic (variability)

High degree of homology in HLA protein sequence

- Represented by dashes in figure

Polymorphic amino acids at certain residues

- May be shared by some alleles
- Give each allele its unique reactivity pattern



Tambur Front. Immun. Aug 2018 (9):2010

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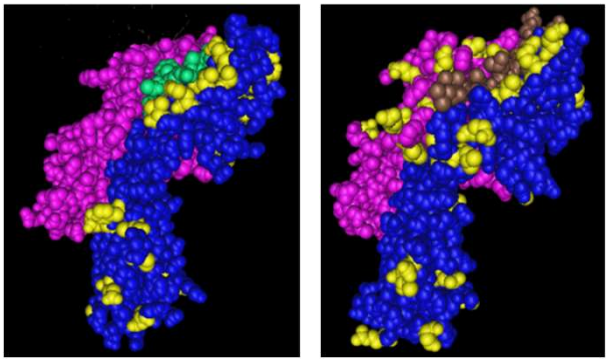
Differences between HLA antigens between donor and recipient defined by polymorphic residues

Polymorphic Residues on HLA-DR and HLA-DQ Molecules



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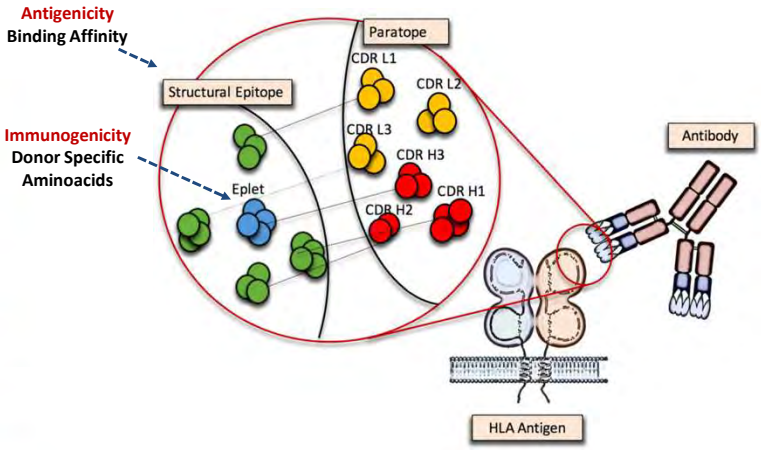
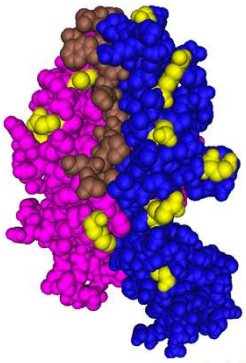
Alloimmune Risk Assessment

HLA Molecular Mismatch induces BCR Allorecognition

Biological Basis is the Epitope – Paratope Structural Relationship





Pediatr Nephrol (2017) 32:1861-69

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HLA Matchmaker

- A molecularly based algorithm for histocompatibility determination
  - Eplet matching for HLA-DR, HLA-DQ, and HLA-DP

Requires High Resolution, Allele level HLA Typing

Patient HLA	Donor HLA	mmEp	Mismatched Donor Eplets
DRB1*1101	DRB1*0405	11	,,12VKH,14HEH, , ,32FYH,34HQ, , ,57SA, ,67LR,71QRA, , , ,96YL,98EN, ,120N, , , ,180LT, ,
DRB1*1302	DRB1*1119	1	, , , , , , , , , , ,67IR, , , , , , , , , , , , ,
DRB3*0101	DRB3*0202	-	, ,
DRB3*0202	DRB4*0101	19	4Q,18L,12AKC,14CEH,16HLW,26WN,32IYN, ,41YNL,48YQ, , ,67LR,71RRA, ,81YV,85VV,96QM,98KNI
DQB1*0301	DQB1*0301	-	, ,
DQB1*0301	DQB1*0302	7	,14GM, ,26L, ,45GV,46GVY, , ,57PA, , , , , , , , , , , , ,167RG, ,185I, , ,
DQA1*0103	DQA1*0302	13	, , ,25YS,34HE,41ER, ,47EQL,48LF,50LF,52FRR,56RR, , , ,75IVR,80IRS, , , , , ,160DD, ,175E,187T
DQA1*0505	DQA1*0505	-	, ,
DPB1*0301	DPB1*0201	-	, , , , , , , , , , , , ,
DPB1*0201	DPB1*2301	3	, , , , , ,55AA,56AE, , , , ,
DPA1*0103	DPA1*0103	-	, , , , , , ,
DPA1*0103	DPA1*0103	-	, , , , , , ,

Duquesnoy and Askar, Human Immunology (2007) 68:12-25

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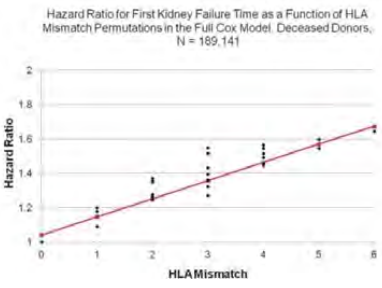
Risk assessment of HLA mismatch

Antigen vs Molecular mismatch

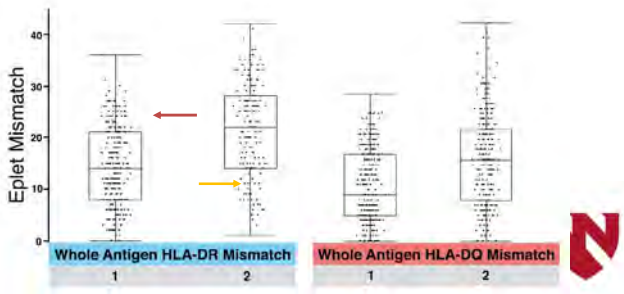
HLA Mismatch increases risk of rejection, DSA, and graft loss



Molecular assessment of HLA eplets may help differentiate degree of mismatch

0, 1, or 2 antigen mismatch

Vs 0 to 40 eplet mismatch



Weibe J Am Soc Nephrol 28: 3353–3362, 2017

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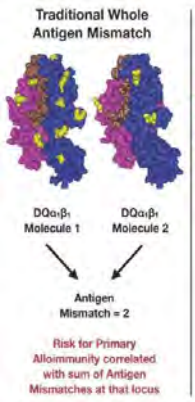
Using class II eplet load to define immunologic risk

Number of Eplet mismatches at a single HLA DR or DQ molecules to assess risk

Figure 2. Three Approaches to Mismatch Quantitation using an HLA-DQ example



*Polymorphic eplets mismatched with donor in yellow (theoretical example), alpha chain is pink, beta chain is blue, peptide is brown

Stratified by DR and DQ mismatch number

- **Low risk**
  - DQ eplet mismatch 0-7 AND DR eplet mismatch 0-8
- **Intermediate risk**
  - HLA DR ≥ 7 or HLA DQ 9-14
- **High risk**
  - HLA DQ ≥ 15 eplet mismatch

Wiebe et al AJT 2019 Jun; 19(6) 1708-1719

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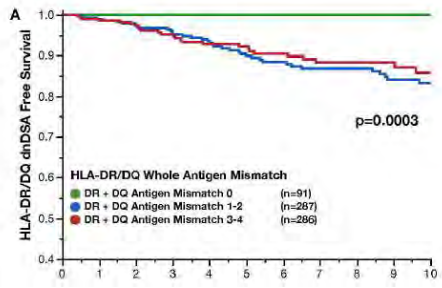
HLA Antigen and eplet mismatch and risk of DSA

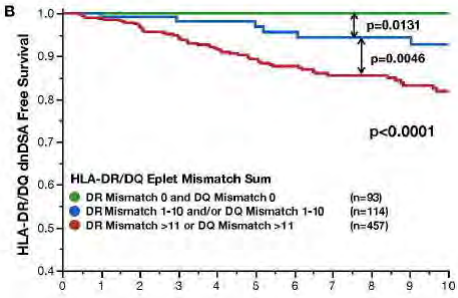
HLA DR and DQ Antigen mismatch

- 0 MM low risk
- Any mismatch > 0 with equal risk



HLA DR and DQ eplet mismatch

- Differentiated risk of DSA with HLA antigen mismatch



Wiebe et al AJT 2019 Jun; 19(6) 1708-1719

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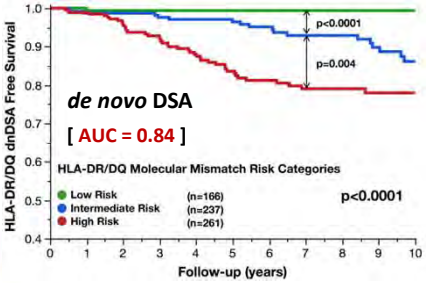
HLA-DR|DQ Molecular Mismatch Score:

Prognostic Biomarker for Primary Alloimmunity in Kidney Transplantation



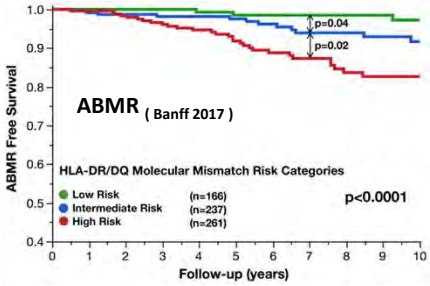
de novo DSA

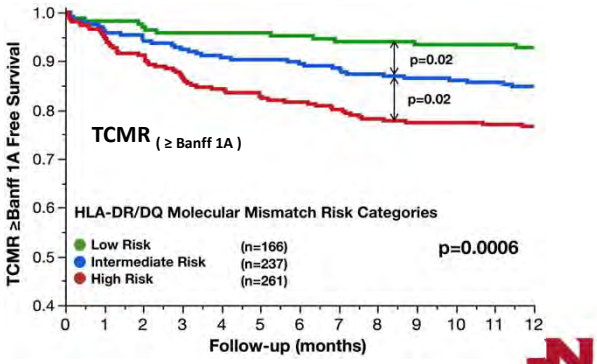
[AUC = 0.84]

Low Risk (25% of transplants)

Intermediate Risk (35% of transplants)

High Risk (40% of transplants)





Wiebe et al., AJT (2019) 19:1708-1719

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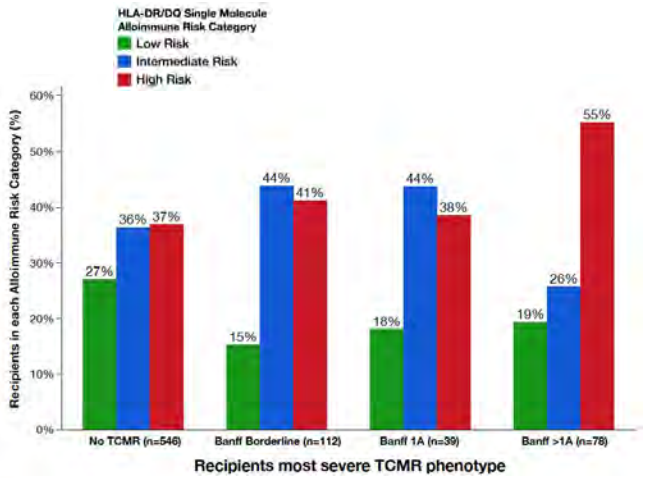
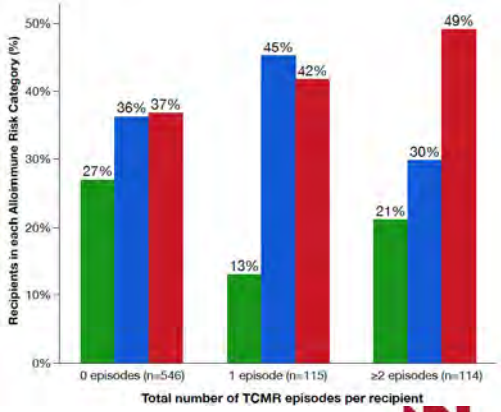
HLA DR/DQ Molecular Mismatch Score Correlates with T-cell Rejection Severity and Refractoriness to Therapy





Rampersad et al, AJT (2022) 22:761-771

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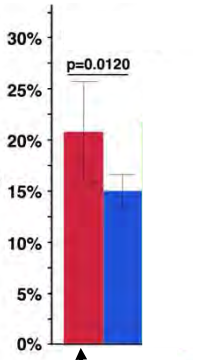
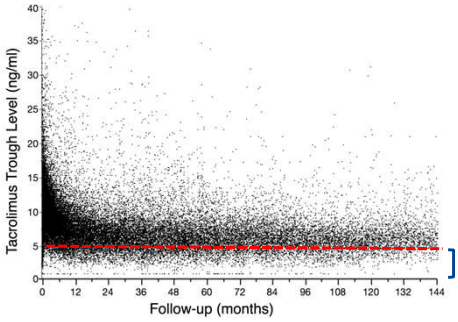
Lower FK levels predicts development of Donor Specific Antibodies

% Tacrolimus Trough Levels < 5ng/ml





Tac C_0 <5 ng/mL

No dnDSA

dnDSA

High Alloimmune Risk
(HLA-DR or DQ Eplet MM >11)

Wiebe et al., JASN (2017) 28:3353-3362

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High immunologic risk patients (defined by eplet mismatch) with low tacrolimus levels at higher risk for developing DSA

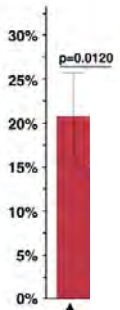
"High risk" Recipients with more DR/DQ eplet mismatches

- "High risk" patients with DSA had higher percentage of low tacrolimus levels

"Low risk" Recipients with less DR/DQ eplet mismatches

- "Low risk" patients did NOT develop DSA with a higher percentage of low tacrolimus levels

% Tacrolimus levels < 5 ng/ml



dnDSA

High Alloimmune Risk
(HLA-DR or DQ Eplet MM >11)

"Tolerated" low FK level

DSA with low FK level

Wiebe et al JASN 2017 28: 3353-3362

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Data showing predictive nature of DR/DQ Molecular matching for rejection, DSA, and graft loss are all Retrospective

RTB-015

ASSESSMENT OF BIOMARKER-GUIDED CNI SUBSTITUTION

IN KIDNEY TRANSPLANTATION

ABCs TRIAL

PETER HEEGER / PETER NICKERSON

National Institute of Allergy and Infectious Diseases

Icahn School of Medicine Mount Sinai

University of Manitoba

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National Institute of Allergy and Infectious Diseases

RTB-015:
ASSESSMENT OF BIOMARKER-GUIDED CNI SUBSTITUTION
(ABCs TRIAL)

Icahn School of Medicine Mount Sinai

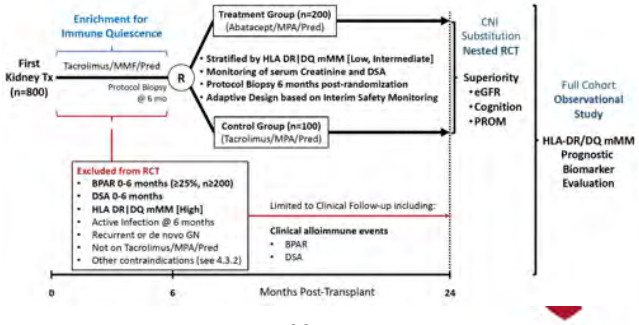
University of Manitoba

Rationale for Study Design

To prospectively test the **prognostic** and **predictive** function of the **HLA mMM biomarker in kidney transplant**

The design includes a **prospective Observational Study** AND **a linked, Nested randomized controlled trial (RCT)**

- In the **Observational Study** we will prospectively validate the **prognostic utility of HLA-DR/DQ mMM** to identify subjects at risk for a primary alloimmune response (Rejection/DSA), AND we will identify immunologically quiescent subjects eligible for the RCT



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National Institute of Allergy and Infectious Diseases

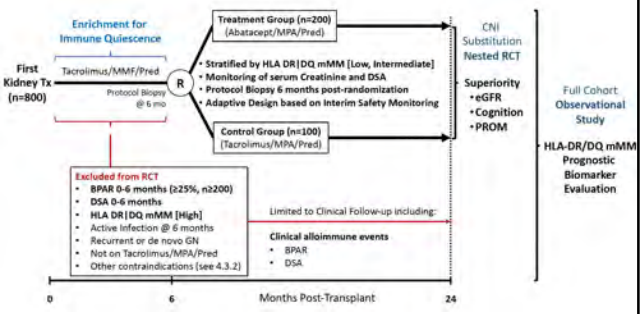
RTB-015:
ASSESSMENT OF BIOMARKER-GUIDED CNI SUBSTITUTION (ABCS TRIAL)

Icahn School of Medicine Mount Sinai

University of Manitoba

NESTED RCT Sub-Study

- Subjects from the Observational Study with Immune Quiescence
  - No DSA and no rejection (including 6 month surveillance biopsy
  - Exclude subjects from the RCT with high DR/DQ mMM score and only include subjects with intermediate or low mMM
- Subjects will be **stratified by HLA DR/DQ mMM category** and randomized to remain on SOC or undergo substitution from CNI to costimulation blockade (abatacept)



Primary Endpoint: eGFR

Secondary Endpoints Cognitive Function

Life Participation PROM, others

We will also evaluate whether HLA mMM strata predict success

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HLA-DR|DQ MOLECULAR MISMATCH SCORE

(Validating a Predictive Biomarker)

National Institute of Allergy and Infectious Diseases

University of Manitoba

Nested RCT Sub-study (modified CTOT-09 design)
(Immune Quiescent @6 mo)

Priority on ↓ Toxicity

R

Stratify by HLA DR|DQ mMM

Abatacept/MMF/Pred (n=**200**)

Tacrolimus/MMF/Pred (n=**100**)

Interim Monitoring

Adaptive Enrichment

Non-Inferiority Primary Endpoint

BPAR Efficacy Failure$_{6\text{-}24\ mo}$

Superiority Secondary Endpoints

- **Renal Function$_{24mo}$**
- **Cognitive Function$_{24\ mo}$**
- **PROM$_{24\ mo}$**

Assessment of Biomarker-guided Calcineurin substitution (ABCs) Trial

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National Institute of Allergy and Infectious Diseases

RTB-015: ASSESSMENT OF BIOMARKER-GUIDED CNI SUBSTITUTION (ABCS TRIAL)

Icahn School of Medicine Mount Sinai

University of Manitoba

- Prospective Observational Study – Determine the PROGNOSTIC and PREDICTIVE ability of HLA DR/DQ molecular mismatch in Kidney Transplantation
- Nested RCT- Determine the ability of the HLA DR/DQ mMM to **PREDICT** who will benefit from CNI substitution with abatacept.

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Personalizing Kidney Transplantation Utilizing Immunologic Risk for Precision Medicine

Alloimmune Risk Assessment at the time of transplant	Transplant	Personalized Immunosuppression Strategy (Predictive Biomarker)	Personalized Allograft Monitoring Strategy (Prognostic Biomarker)
Donor Specific Memory Risk • Solid Phase DSA screen • Sensitization history	High Risk	AVOID (KPD) vs. Desensitization Induction (depletional) Standard Dose TAC	↑ frequency blood/urine biomarker screening ↑ frequency surveillance Biopsies Monitor Creatinine and TAC C_0 levels
	High Risk	Induction Therapy (anti-IL2R mAb) Std Dose TAC/MPA/Pred	
Primary Alloimmune Risk • HLA DR|DQ molecular MM • Recipient Age	Intermediate	+/- Induction Therapy Std Dose TAC, minimization/MPA	Limited blood/urine biomarker screening Monitor Creatinine and TAC C_0 levels
	Low Risk	Low Dose TAC/MPA	Monitor Creatinine and TAC C_0 levels

Wiebe and Nickerson, JASN 2020;31:1921-1925
Tambur et al., AJT 2018;18:1604-1614

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Next Steps

- Identify HLA mismatch epitopes that drive immunogenicity
  - Number of mismatches
  - Location of mismatches
  - Nature of mismatched epitopes
- Clinical Trials to test hypothesis
  - Immunosuppression modification/minimization
- Allocation optimization?

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