

Gene Expression Profiling Advantages and Disadvantages of Monitoring Immune Activity Rather than Injury

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CUTTING EDGE of TRANSPLANTATION

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NO SIZE FITS ALL: Uncovering the Potential of Personalized Transplantation

Disclosure

No disclosures.

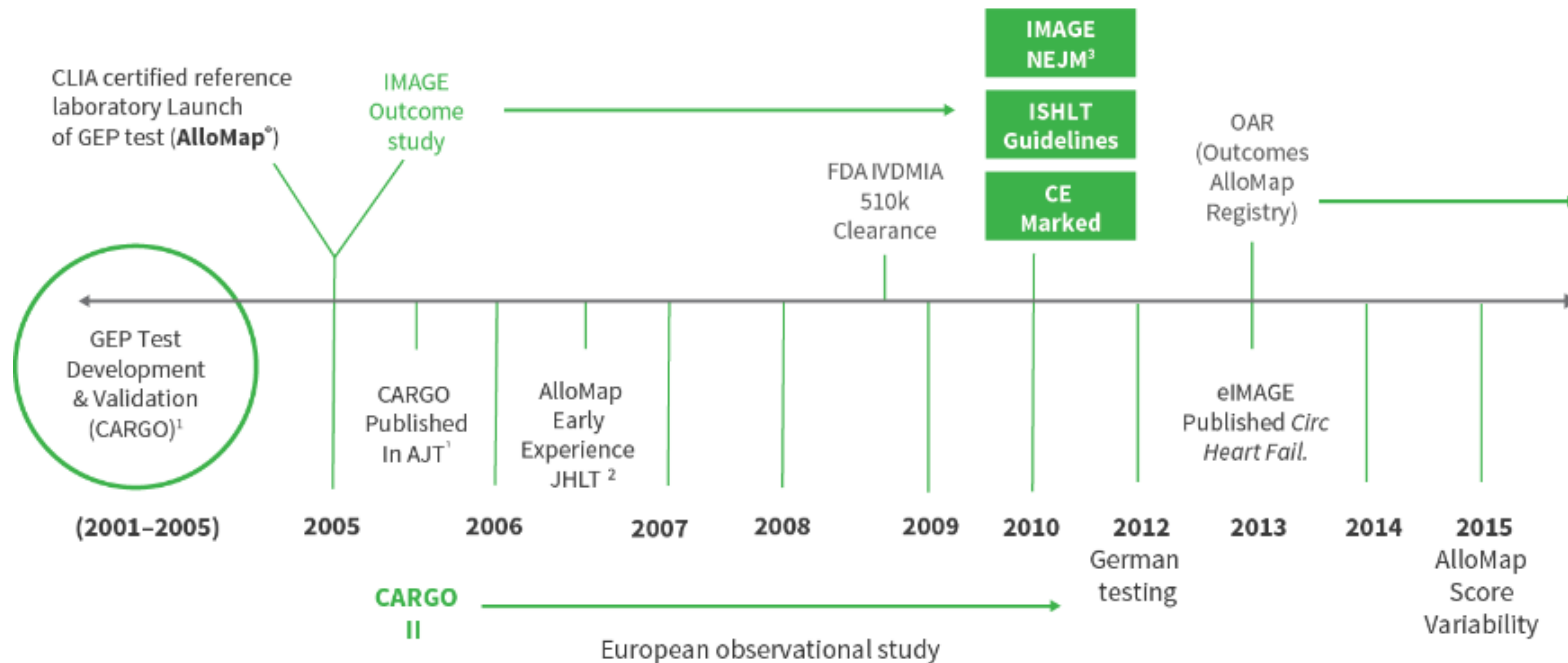
Learning Objectives

1. To review peripheral blood gene expression profiling studies for monitoring immune activity to discriminate cellular rejection in cardiac transplant recipients.
2. To be familiar with recent studies of gene expression profiling of allograft biopsy samples to diagnose acute cellular, antibody mediated rejection as well as injury.
3. To discuss advantages and disadvantages of monitoring immune activity rather than injury.

Cardiac Transplant Immune Activation

- Heart transplant rejection remains one of the main complications limiting graft/recipient survival
- Serial invasive EMB remains the ‘gold standard’ for rejection diagnosis
- Histological grading has significant interobserver variability, high rate of false positive and negative results

The AlloMap™ genomic biomarker story: 10 years after



Deng, Clin Transplant 2017

Cardiac Allograft Rejection Gene Expression Observational (CARGO) Study

- Multicenter study of paired gene expression studies and biopsy samples.
- 11 genes identified that were differentially expressed in the setting of acute rejection.
- Algorithm used to yield a single score (range 0-40), with a score of ≥ 34 indicating higher likelihood of acute cellular rejection.

AJT 2006; 6:150-60

IMAGE Trial

- Invasive Monitoring through Gene Expression (IMAGE) was a randomized trial of 600 patients, at least 6 months post transplant, which showed non-inferiority of a GEP strategy as compared to a biopsy-driven protocol.

NEJM 2010;362:1890-900

CARGO II Study

- Multicenter study of AlloMap® comparing GEP to biopsy conducted in Europe validated results of CARGO Trial.
- Showed GEP scores rise and then stabilize during the first year post-transplant.

Eur Heart J 2016;37:2591-601

Early Invasive Monitoring Attenuation through Gene Expression (EIMAGE) Study

- Single center study of 60 patients randomized to AlloMap[®] GEP or biopsy starting at 55 days post-transplant.
- Outcomes with GEP surveillance were non-inferior to outcomes with biopsy surveillance in low risk patients.

Circ Heart Fail. 2015;8:557-64

AlloMap Score Variability (AMV)

- AMV defined as the SD of four AlloMap scores collected at least ≥ 315 days post-transplant.
- In a retrospective analysis of CARGO II Trial defining adverse events as death, retransplant or graft failure.
- NPV with AMV score of 0.6 was 97% (95% CI 91.4-100)
- PPV for AMV of 1.5 was 35.4% (95% CI 13.5-75.8)

BMC Cardiovasc Disord 2015;15:120

The Outcome AlloMap Registry (OAR)

- Observational, multicenter prospective study of 1504 heart transplant recipients.
- Largest contemporary cohort of patients undergoing GEP for surveillance.
- Among patients selected for GEP surveillance, survival was excellent and rates of acute rejection, graft dysfunction, readmission and death low.
- At 2-6 months, GEP score ≤ 30 had NPV 98.4%. After 6 months, GEP score ≤ 34 had NPV of 98.5%.

JHLT 2019;38:51-58

- Patterns of gene expression in high GEP score samples correlated with clinical factors in the Outcomes AlloMap Registry.
- Higher rates of hospitalization since prior visit in inflammation (25%) and T cell groups (27%) mostly due to infection, compared to lower rates for other gene groups.

JHLT 2018;37:S49

GEP Variability score (GVS)

- Low variability in GEP scores are associated with decreased adverse events post-transplant.
- GEP Variability score (GVS) based on 3 consecutive GEP scores beginning six months post-transplant can predict IMAGE Outcomes plus MI and PCI post-transplant. $GVS < 0.6$ was associated with low risk.

JHLT 2018;37:S330

Advantages of monitoring Immune activity rather than Injury

- Multiple clinical trials demonstrating utility for monitoring acute cellular rejection
- AlloMap[®] commercially available
- ISHLT guideline recommendation (Grade IIa, level of evidence B)
- Peripheral blood GEP advantages – Noninvasive, decrease in number of biopsies, high negative predictive value, assist steroid taper.

Disadvantages of Monitoring Immune Activity rather than Injury

- Low positive predictive value, investigated in low risk patients.
- Inaccuracy with concurrent high dose steroids.
- High scores in presence of CMV.
- Relationship to cardiac function, hemodynamics, restrictive and diastolic patterns not demonstrated.

Gene Expression Profiling in Heart Transplant in biopsies with AMR

- First study of molecular approach in biopsies to refine the diagnosis and characterize potential mechanism of AMR.
- 71 biopsy samples from 55 patients diagnosed with AMR using histology compared with matched controls of 55 rejection free and ACR patients to eliminate any overlap in gene expression between the two types of rejection.

Circulation 2017;135:917-935

Gene Expression Profiling in Heart Transplant biopsies with AMR

- The presence of AMR was accurately determined by molecular approach in EMB specimens, which correlated with degree of injury and disease activity.
- AMR had a distinct molecular pattern of injury driven mainly by NK cell burden, endothelial cell activation, macrophage burden, and interferon- γ -inducible effects.

Circulation 2017;135:917-935

Grade	Definition	Substrates
pAMR 0	Negative for pathologic AMR	Histologic and immunopathologic studies are both negative.
pAMR 1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic findings are negative.
pAMR 1 (I+)	Immunopathologic AMR alone	Histologic findings are negative and immunopathologic findings are positive (CD68+ and/or C4d+).
pAMR 2	Pathologic AMR	Histologic and immunopathologic findings are both present.
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema and immunopathologic findings are present. These cases may be associated with profound hemodynamic dysfunction and poor clinical outcomes.

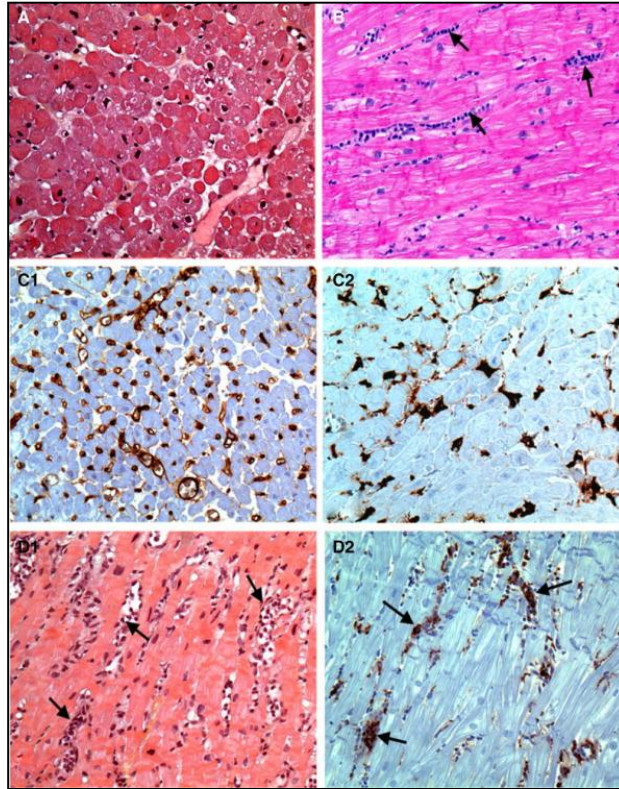
AMR indicates antibody-mediated rejection; and ISHLT, International Society of Heart and Lung Transplantation.
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Table. The 2013 ISHLT Working Formulation for Pathological Diagnosis of Cardiac Antibody-Mediated Rejection

The Search for a Gold Standard to Detect Rejection in Heart Transplant Patients: Are We There Yet?
Kobashigawa, Jon

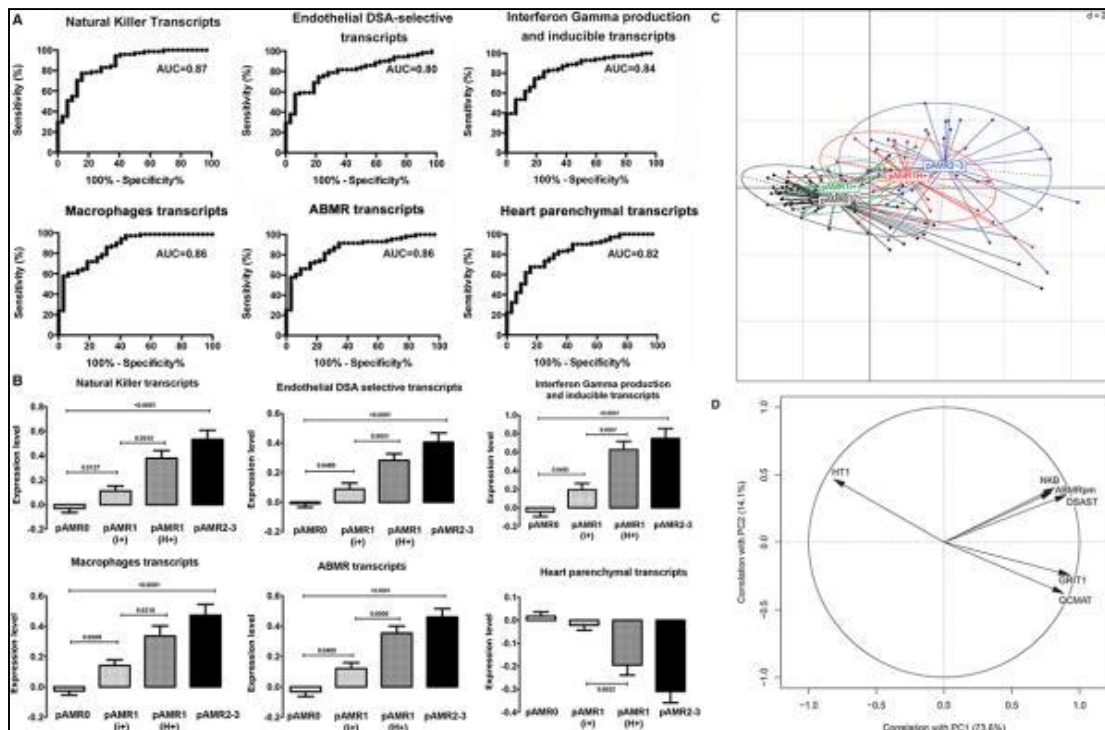
Circulation. 135(10):936-938, March 7, 2017.
DOI: 10.1161/CIRCULATIONAHA.117.026752

Histology of Heart AMR



Circulation. 135(10):917-935, 2017.

Gene Expression Profiling for the Identification and Classification of Antibody-Mediated Heart Rejection



Intragraft expression of the pathogenesis-based transcripts and relationship to antibody-mediated rejection, diagnostic activity, and stage.

Circulation. 135(10):917-935, 2017.

CARDIAC ALLOGRAFT INJURY

- There are distinct causes of injury with importance that varies at different times after transplant.
- Response to injury in heart parenchyma has been explored in biopsies expressing molecular transcripts reflecting injury.
- Biopsies with molecular injury but no molecular rejection were often misdiagnosed rejection by histology.

Halloran JCI Insight 2018

Advantages of Monitoring Injury

- Molecular injury in heart transplant is strongly associated with rejection and predicted graft failure, whereas histologic ACR or AMR was not predictive.
- In multivariate analysis, molecular rejection and injury were the only significant hazards for graft loss at 3 years post transplant.

Abstract 170, AST 2018

Cardiac Allograft Injury

- Changes in gene expression signatures will likely emerge as important surrogate end points for chronic injury intervention trials.
- Effects of early post transplant events (ischemia/reperfusion injury and innate immunity) on chronic injury remains to be explored further.

Cardiac Allograft Injury

- Histology has limited ability to assess injury, potentially confusing it with rejection.
- Molecular transcripts reflecting injury in addition to evaluating transcripts for ACR and AMR reflect donation-implantation injury.
- Transcripts for both injury and ACR were associated with reduced LVEF.

Halloran JCI Insight 2018

Allograft Injury monitoring disadvantages

- Recent molecular transcript data exciting!
Await large prospective clinical trial results.
- Mechanisms of association of injury in acute rejection to be elucidated.
- Long term follow up required of early molecular markers of graft injury and failure, allograft injury mechanisms to be identified.

Towards a Complete Transformation of the Approach to Heart Transplantation

Today's Care

Routine EMB (invasive, expensive, variable) by protocol/for cause



Protocol Immunosuppression



Future Care

Gene Expression Profiling with integration of markers of injury, EMB, clinical, hemodynamics and functional information.

Precision immunosuppression, individualized risk analysis, new targets for therapy

